* * * * * * * * * * Welcome to STN International * * * * * * * * * *

NEWS 1		Web Page URLs for STN Seminar Schedule - N. America
NEWS 2		"Ask CAS" for self-help around the clock
NEWS 3	SEP 09	CA/CAplus records now contain indexing from 1907 to the present
NEWS 4	DEC 08	INPADOC: Legal Status data reloaded
NEWS 5	SEP 29	DISSABS now available on STN
NEWS 6	OCT 10	PCTFULL: Two new display fields added
NEWS 7	OCT 21	BIOSIS file reloaded and enhanced
NEWS 8	OCT 28	BIOSIS file segment of TOXCENTER reloaded and enhanced
NEWS 9	NOV 24	MSDS-CCOHS file reloaded
NEWS 10	DEC 08	CABA reloaded with left truncation
NEWS 11	DEC 08	IMS file names changed
NEWS 12	DEC 09	Experimental property data collected by CAS now available in REGISTRY
NEWS 13	DEC 09	STN Entry Date available for display in REGISTRY and CA/CAplus
NEWS 14	DEC 17	DGENE: Two new display fields added
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NEWS 16	DEC 19	CROPU no longer updated; subscriber discount no longer available
NEWS 17	DEC 22	Additional INPI reactions and pre-1907 documents added to CAS databases
NEWS 18	DEC 22	IFIPAT/IFIUDB/IFICDB reloaded with new data and search fields
NEWS 19	DEC 22	ABI-INFORM now available on STN
NEWS 20	JAN 27	Source of Registration (SR) information in REGISTRY updated and searchable
NEWS 21	JAN 27	A new search aid, the Company Name Thesaurus, available in CA/CAplus
NEWS 22	FEB 05	German (DE) application and patent publication number format changes
NEWS 23	MAR 03	MEDLINE and LMEDLINE reloaded
NEWS 24	MAR 03	MEDLINE file segment of TOXCENTER reloaded
NEWS 25	MAR 03	FRANCEPAT now available on STN
NEWS 26	MAR 29	Pharmaceutical Substances (PS) now available on STN
NEWS 27	MAR 29	WPIFV now available on STN
NEWS 28	MAR 29	No connect hour charges in WPIFV until May 1, 2004
NEWS 29	MAR 29	New monthly current-awareness alert (SDI) frequency in RAPRA

NEWS EXPRESS	MARCH 31 CURRENT WINDOWS VERSION IS V7.00A, CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP), AND CURRENT DISCOVER FILE IS DATED 3 MARCH 2004
NEWS HOURS	STN Operating Hours Plus Help Desk Availability
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	ENTRY	SESSION
FULL ESTIMATED COST	0.21	0.21

FILE 'MEDLINE' ENTERED AT 08:27:59 ON 06 APR 2004

FILE 'EMBASE' ENTERED AT 08:27:59 ON 06 APR 2004

FILE 'BIOSIS' ENTERED AT 08:27:59 ON 06 APR 2004

FILE 'SCISEARCH' ENTERED AT 08:27:59 ON 06 APR 2004

FILE 'CAPLUS' ENTERED AT 08:27:59 ON 06 APR 2004

=> s "AVP"
L1 30695 "AVP"

=> s l1 and "PTHrP"
L2 29 L1 AND "PTHRP"

=> dup remove l2
PROCESSING COMPLETED FOR L2
L3 7 DUP REMOVE L2 (22 DUPLICATES REMOVED)

=> d l3 1-7 cbib abs

L3 ANSWER 1 OF 7 MEDLINE on STN DUPLICATE 1
2003282974. PubMed ID: 12810532. Centrally administered tuberoinfundibular peptide of 39 residues inhibits arginine vasopressin release in conscious rats. Sugimura Yoshihisa; Murase Takashi; Ishizaki Seiji; Tachikawa Kazushige; Arima Hiroshi; Miura Yoshitaka; Usdin Ted B; Oiso Yutaka. (Department of Internal Medicine, Graduate School of Medicine, Nagoya University, Nagoya, Aichi 466-8550, Japan.) Endocrinology, (2003 Jul) 144 (7) 2791-6. Journal code: 0375040. ISSN: 0013-7227. Pub. country: United States. Language: English.

AB Tuberoinfundibular peptide of 39 residues (TIP39) is a recently discovered neuropeptide identified on the basis of its ability to activate the PTH2 receptor, and it is thought to be the brain PTH2 receptor's endogenous ligand. The PTH2 receptor is highly expressed in the hypothalamus, suggesting a role in the modulation of neuroendocrinological functions. **PTHrP**, which also belongs to the PTH-related peptides family, stimulates arginine vasopressin (**AVP**) release. In the present study, therefore, we investigated the effect of centrally administered TIP39 on **AVP** release in conscious rats. Intracerebroventricular administration of TIP39 (10-500 pmol/rat) significantly suppressed the plasma **AVP** concentration in dehydrated rats, and the maximum effect was obtained 5 min after administration (dehydration with 100 pmol/rat TIP39, 4.32 +/- 1.17 pg/ml; vs. control, 8.21 +/- 0.70 pg/ml). The plasma **AVP** increase in response to either hyperosmolality [ip injection of hypertonic saline (HS), 600 mosmol/kg] or hypovolemia [ip injection of polyethylene glycol (PEG)] was also significantly attenuated

suggest that ... and baroregulation of **AVP** release and that intrinsic opioid systems are involved in its mechanism.

L3 ANSWER 2 OF 7 MEDLINE on STN DUPLICATE 2

2002193451. PubMed ID: 11897711. The mutual regulation of arginine-vasopressin and **PTHrP** secretion in dissociated supraoptic neurons. Yamamoto Shigeki; Morimoto Isao; Tanaka Yoshiya; Yanagihara Nobuyuki; Eto Sumiya. (Department of Internal Medicine, Mitsubishikagaku Hospital, Kitakyushu 806-0037, Japan.. 5308940@cc.m-kagaku.co.jp) . Endocrinology, (2002 Apr) 143 (4) 1521-9. Journal code: 0375040. ISSN: 0013-7227. Pub. country: United States. Language: English.

AB **PTHrP** is detected in the supraoptic nucleus (SON) and paraventricular nucleus. We have recently demonstrated that **PTHrP** (1-34) is involved in **AVP** release and synthesis in the SON in vivo and in vitro. **PTHrP** and **AVP**, which act on blood vessels, may interact by autocrine and paracrine mechanisms in the central nervous system. The present study was undertaken to determine the mutual regulation of **AVP** and **PTHrP** secretion in dissociated magnocellular neurons of the SON. Both **AVP** and **PTHrP** existed in the dissociated SON neurons by immunohistochemistry. **PTHrP**(1-34) stimulated **AVP** secretion from the cells dose dependently, but **PTHrP**(7-34) and PTH(1-34) did not. **PTHrP**(1-34)-stimulated **AVP** secretion was associated with cAMP generation. **PTHrP**(1-34)-induced cAMP generation was inhibited by a 100-fold molar excess of **PTHrP**(7-34) but not by that of PTH(1-34). **PTHrP**(1-34) also stimulated **AVP** mRNA expression in the cells. These results are consistent with our previous observations that **PTHrP**(1-34) is involved in **AVP** secretion through a receptor distinct from type I PTH/ **PTHrP** receptor. Next, **AVP** stimulated dose-dependent **PTHrP** release from the dissociated SON neurons. The **AVP** -induced **PTHrP** release was suppressed by both OPC-21268 (V(1a) receptor antagonist) and dP[Thy(Me)(2)]**AVP** (V(1a)/V(1b) receptor antagonist) but not by OPC-31260 (V(2) receptor antagonist). **AVP** increased PKC activity dose dependently but not cAMP generation in the SON neurons. The **AVP**-stimulated **PTHrP** release was blocked by staurosporine (PKC inhibitor), nicardipine (L-type calcium channel blocker) or omega-agatoxin IVA (N type). Furthermore, **AVP** stimulated **PTHrP** mRNA expression for 12 h in the SON neurons. These results indicate that **AVP** caused increases in **PTHrP** secretion and its mRNA levels through V(1a) and/or V(1b) receptors in the SON neurons. Our observations, taken together, suggest that **PTHrP** stimulates **AVP** secretion into the extracellular space of the SON, which in turn leads to further secretion of **AVP** and **PTHrP** by an autocrine/paracrine mechanism.

L3 ANSWER 3 OF 7 CAPLUS COPYRIGHT 2004 ACS on STN

2001:828415 Document No. 137:89412 Detection of variations in the DNA methylation profile of genes in the determining the risk of disease. Berlin, Kurt; Piepenbrock, Christian; Olek, Alexander (Epigenomics A.-G., Germany). PCT Int. Appl. WO 2001077373 A2 20011018, 636 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, ...

The invention further relates to the use of the same for determining the gene variant with regard to DNA methylation, a medical device, using an oligonucleotide kit, a method for determining the methylation state of an individual and a method for the establishment of a model for establishing the probability of onset of a disease state in an individual. Such diseases may be: undesired pharmaceutical side-effects; cancerous diseases; CNS dysfunctions, injuries or diseases; aggressive symptoms or relational disturbances; clin., psychol. and social consequences of brain injury; psychotic disorders and personality disorders; dementia and/or associated syndromes; cardiovascular disease, dysfunction and damage; dysfunction, damage or disease of the gastrointestinal tract; dysfunction, damage or disease of the respiratory system; injury, inflammation, infection, immunity and/or anastasis; dysfunction, damage or disease of the body as an abnormal development process; dysfunction, damage or disease of the skin, muscle, connective tissue or bones; endocrine and metabolic dysfunction, damage or disease; headaches or sexual dysfunction. This abstract record is one of several records for this document necessitated by the large number of index entries required to fully index the document and publication system constraints.

L3 ANSWER 4 OF 7 MEDLINE on STN DUPLICATE 3

1998081790. PubMed ID: 9421437. Centrally administered parathyroid hormone (PTH)-related protein(1-34) but not PTH(1-34) stimulates arginine-vasopressin secretion and its messenger ribonucleic acid expression in supraoptic nucleus of the conscious rats. Yamamoto S; Morimoto I; Zeki K; Ueta Y; Yamashita H; Kannan H; Eto S. (First Department of Internal Medicine, School of Medicine, University of Occupational and Environmental Health, Kitakyushu, Japan.) Endocrinology, (1998 Jan) 139 (1) 383-8. Journal code: 0375040. ISSN: 0013-7227. Pub. country: United States. Language: English.

AB It has been suggested that PTH-related protein (**PTHrP**) is an endogenous modulator of cardiovascular systems. We have reported that **PTHrP**(1-34), but not PTH(1-34), causes the release of arginine-vasopressin (**AVP**) from the supraoptic nucleus (SON) of the hypothalamus in vitro through a novel receptor distinct from the PTH/**PTHrP** receptors (type I or type II) described previously. In this study, we have investigated the in vivo effects of **PTHrP**(1-34) on **AVP** secretion and its, messenger RNA (mRNA) expression in the SON in conscious rats. Intracerebroventricular (i.c.v.) administration of **PTHrP**(1-34) resulted in an increase in plasma **AVP** concentration in a dose-dependent manner (0-400 pmol/rat). The maximal effect was obtained at 15 min after i.c.v. administration of **PTHrP** (1-34). Neither **PTHrP**(7-34) nor PTH(1-34) had any effect on plasma **AVP** levels. **PTHrP**(1-34)-induced **AVP** secretion was antagonized by pretreatment with **PTHrP**(7-34) but not by that with PTH(1-34). In addition, in situ hybridization study revealed that **AVP** mRNA expression in the SON and paraventricular nucleus was significantly increased 30 min after i.c.v. administration of **PTHrP**(1-34) and reached a maximum at 180 min. Furthermore, in Northern blot analyses, **AVP** mRNA expression in the SON was increased to approximately a 2-fold of basal level by **PTHrP** (1-34). On the other hand, neither **PTHrP**(7-34) or PTH(1-34) had any effect on the mRNA expression. The **PTHrP**(1-34)-stimulated **AVP** mRNA expression was eliminated by pretreatment with **PTHrP**(7-34) but not with PTH(1-34). These results suggest that, in the central nervous system, **PTHrP**(1-34) is involved in

PTHrP (1-34)] induces vasorelaxation ... nucleus in vitro through a novel receptor distinct from a type I or type II PTH/**PTHrP** receptor. Yamamoto S; Morimoto I; Yanagihara N; Zeki K; Fujihira T; Izumi F; Yamashita H; Eto S. (First Department of Internal Medicine, School of Medicine, University of Occupational and Environmental Health, Yahatanishi-ku, Kitakyushu, Japan.) Endocrinology, (1997 May) 138 (5) 2066-72. Journal code: 0375040. ISSN: 0013-7227. Pub. country: United States. Language: English.

AB PTH and PTH-related peptide (**PTHrP**) bind to a type I PTH/**PTHrP** receptor expressed in bone and kidney or a type II receptor in nonclassical target tissue with equal affinity and similar bioactivities. **PTHrP** is abundant in the central nervous system, but its physiological role remains unknown. Herein, we examined the role of **PTHrP**-(1-34) on arginine vasopressin (**AVP**) release from the rat supraoptic nucleus (SON). Application of **PTHrP**-(1-34) to SON slices caused an increase in **AVP** release in a concentration-dependent manner. Neither **PTHrP**-(7-34) nor PTH-(1-34) had any effect on **AVP** release from the SON. **PTHrP**-(1-34)-induced **AVP** release was antagonized by a large excess of **PTHrP**-(7-34) and by H89, an inhibitor of cAMP-dependent protein kinase (A kinase), but not by PTH-(1-34) or PTH-(13-34). **PTHrP**-(1-34), but not PTH-(1-34), also dose-dependently increased the levels of cAMP in the SON. 125I-Labeled **PTHrP**-(1-34) bound specifically to crude membranes isolated from the SON. Scatchard analysis showed a single class of binding sites for **PTHrP**-(1-34) with a Kd of 36.4 nM and a maximum binding capacity of 3.94 pmol/mg protein. No specific binding for 125I-labeled PTH-(1-34) was noted. The binding of 125I-labeled **PTHrP**-(1-34) was displaced by unlabeled **PTHrP**-(1-34) and unlabeled **PTHrP**-(7-34), but not by unlabeled PTH-(1-34). These findings suggest that **PTHrP**-(1-34), but not PTH-(1-34), causes the release of **AVP** from the SON through a novel receptor distinct from type I or II PTH/**PTHrP** receptors.

L3 ANSWER 6 OF 7 MEDLINE on STN DUPLICATE 5

94309285. PubMed ID: 7518545. Cardiovascular effects of human parathyroid hormone and parathyroid hormone-related peptide. Shan J; Pang P K; Lin H C; Yang M C. (Department of Physiology, University of Alberta, Edmonton, Canada.) Journal of cardiovascular pharmacology, (1994) 23 Suppl 2 S38-41. Journal code: 7902492. ISSN: 0160-2446. Pub. country: United States. Language: English.

AB Parathyroid hormone (PTH) is hypotensive in mammals and is a potent coronary vasodilator. Parathyroid hormone-related peptide (**PTHrp**) has been reported to have similar vascular activity. In the present study, the effects of human PTH (hPTH) and human **PTHrp** (hPTHrp) were compared in various in vivo and in vitro assays. In vivo studies included blood pressure measurement and coronary blood flow determination with labeled microspheres in anesthetized and cannulated normotensive rats. Isolated rat tail artery and portal vein helical strips were used in studying tension development in vitro. In the blood pressure assay, **PTHrp** was several times more potent than PTH. **PTHrp** was also significantly more potent than PTH in relaxing tail artery precontracted with arginine vasopressin (**AVP**). **PTHrp** and PTH both inhibited the spontaneously contracting portal vein, but again **PTHrp** was significantly more potent. **PTHrp** (1 microgram/kg) produced a greater increase in coronary blood flow as compared with the same dose of PTH. These data suggest that **PTHrp**

forms of essential hypertension, [illegible]
may be responsible.

L3 ANSWER 7 OF 7 MEDLINE on STN DUPLICATE 6
94037644. PubMed ID: 8222337. Effect of arginine vasopressin and parathyroid hormone-related protein on renal function in the ovine foetus. Horne R S; MacIsaac R J; Moritz K M; Tangalakis K; Wintour E M. (Howard Florey Institute of Experimental Physiology and Medicine, University of Melbourne, Parkville, Australia.) Clinical and experimental pharmacology & physiology, (1993 Sep) 20 (9) 569-77. Journal code: 0425076. ISSN: 0305-1870. Pub. country: Australia. Language: English.
AB 1. The effects of intravenous infusions of arginine vasopressin (**AVP**), parathyroid hormone-related protein (**PTHrP**) and **AVP+PTHrP** on renal function in intact ovine foetuses at 100-125 days of gestation were examined. 2. A low dose of **AVP** (5.5 +/- 0.9 pmol/h) increased plasma **AVP** concentrations from 0.6 pmol/L to 2.1 +/- 0.4 pmol/L (mean +/- s.e.m; n = 8). This dose caused a significant reduction in free water clearance (CH2O; P < 0.001), without any significant change in fetal arterial blood pressure, glomerular filtration rate (GFR), or the urinary excretion rates of sodium, calcium or 3',5'-cyclic adenosine monophosphate (cAMP). 3. Infusions of **PTHrP** (1 nmol/h), with or without 1 nmol bolus dose, significantly increased (P < 0.05) urine osmolality (UOSM), but did not synergize with **AVP** in reducing CH2O. 4. It is concluded that **AVP** and **PTHrP** do not act synergistically on the kidney of the intact ovine foetus.

=> s anti-PTHrP
L4 200 ANTI-PTHRP

=> s l4 and "AVP"
L5 0 L4 AND "AVP"

=> s l4 and vasopressin
L6 0 L4 AND VASOPRESSIN

=> s l4 and vomiting
L7 3 L4 AND VOMITING

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PROCESSING COMPLETED FOR L7
L8 1 DUP REMOVE L7 (2 DUPLICATES REMOVED)

=> d l8 cbib abs

L8 ANSWER 1 OF 1 MEDLINE on STN DUPLICATE 1
2001460865. PubMed ID: 11506305. Primary adenosquamous carcinoma of the liver which produces granulocyte-colony-stimulating factor and parathyroid hormone related protein: association with leukocytosis and hypercalcemia. Hayashi T; Mizuki A; Yamaguchi T; Hasegawa T; Kunihiro T; Tsukada N; Matsuoka K; Orikasa H; Yamazaki K. (Department of Internal Medicine, Tokyo Saiseikai Central Hospital.) Internal medicine (Tokyo, Japan), (2001 Jul) 40 (7) 631-4. Journal code: 9204241. ISSN: 0918-2918. Pub. country: Japan. Language: English.
AB A 55-year-old man was admitted to our hospital with fever and **vomiting**. Abdominal computed tomography (CT) revealed multiple

demonstrated positive cytoplasmic immunohistochemistry staining with anti-G-CSF and **anti-PTHrP** antibodies. This result suggested that the tumor produced G-CSF and PTHrP.

=> s l4 and polyuria
L9 3 L4 AND POLYURIA

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L10 1 DUP REMOVE L9 (2 DUPLICATES REMOVED)

=> d l10 cbib abs

L10 ANSWER 1 OF 1 MEDLINE on STN DUPLICATE 1
2003534792. PubMed ID: 14613038. Treatment of malignancy-associated hypercalcemia and cachexia with humanized anti-parathyroid hormone-related protein antibody. Sato Koh; Onuma Etsuro; Yocum Richard C; Ogata Etsuro. (Department of International Coordination, Chugai Pharmaceutical Co, Ltd, Skizuuoka, Japan.) Seminars in oncology, (2003 Oct) 30 (5 Suppl 16) 167-73. Ref: 11. Journal code: 0420432. ISSN: 0093-7754. Pub. country: United States. Language: English.

AB Parathyroid hormone-related protein (PTHrP) plays a central role in humoral hypercalcemia of malignancy (HHM), which is one of the most frequent paraneoplastic syndromes. PTHrP produced by the tumor acts through a common PTH/PTHrP receptor to promote bone resorption, inhibit calcium excretion from the kidney, and induce hypercalcemia. Patients with HHM often develop cachexia associated with typical symptoms such as anorexia, malaise, nausea, constipation, **polyuria**, polydipsia, and confusion. The etiology of the cachexia is not fully understood but is thought to be caused by hypercalcemia and various cytokines such as interleukin-6, tumor necrosis factor-alpha, leukemia inhibitory factor, and others. In this study, we investigated the role of PTHrP in hypercalcemia and cachexia in HHM by using humanized **anti-PTHrP** antibody. A mouse monoclonal antibody that binds to PTHrP amino acid sequence 1-34 and inhibits PTHrP function has been humanized to create a specific and potent agent for the treatment of patients with HHM. The mouse monoclonal antibody has been shown to have antihypercalcemic activity against nude mice bearing human tumors. Because a mouse antibody is highly immunogenic in human patients, the complementarity-determining regions from the mouse antibody were grafted into a human antibody. The resulting humanized antibody specifically recognizes PTHrP(1-34) and neutralizes PTHrP functions in vitro and in vivo. The humanized **anti-PTHrP** antibody was administered intravenously to HHM model animals bearing tumors such as LC-6 human lung carcinoma. These animals showed symptoms similar to those of patients with HHM (eg, hypercalcemia and cachexia). The humanized **anti-PTHrP** antibody-treated animals responded with normalization of blood ionized calcium level through an improvement of bone metabolism and calcium excretion. Moreover, the treated animals also showed an improvement in body weight, ultromotivity, metabolic alkalosis, food consumption, water intake, serum phosphorus, and renal function. Consequently, the humanized antibody-treated animals experienced complete resolution of hypercalcemia and cachexia. These results suggest that the humanized antibody would be an effective and beneficial agent for patients with HHM, and that PTHrP is a major pathogenetic factor of hypercalcemia and cachexia in patients with

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L12 1 DUP REMOVE L11 (2 DUPLICATES REMOVED)

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L12 ANSWER 1 OF 1 MEDLINE on STN DUPLICATE 1
2003534792. PubMed ID: 14613038. Treatment of malignancy-associated hypercalcemia and cachexia with humanized anti-parathyroid hormone-related protein antibody. Sato Koh; Onuma Etsuro; Yocum Richard C; Ogata Etsuro. (Department of International Coordination, Chugai Pharmaceutical Co, Ltd, Skizuuoka, Japan.) Seminars in oncology, (2003 Oct) 30 (5 Suppl 16) 167-73. Ref: 11. Journal code: 0420432. ISSN: 0093-7754. Pub. country: United States. Language: English.

AB Parathyroid hormone-related protein (PTHrP) plays a central role in humoral hypercalcemia of malignancy (HHM), which is one of the most frequent paraneoplastic syndromes. PTHrP produced by the tumor acts through a common PTH/PTHrP receptor to promote bone resorption, inhibit calcium excretion from the kidney, and induce hypercalcemia. Patients with HHM often develop cachexia associated with typical symptoms such as anorexia, malaise, nausea, constipation, polyuria, polydipsia, and confusion. The etiology of the cachexia is not fully understood but is thought to be caused by hypercalcemia and various cytokines such as interleukin-6, tumor necrosis factor-alpha, leukemia inhibitory factor, and others. In this study, we investigated the role of PTHrP in hypercalcemia and cachexia in HHM by using humanized **anti-PTHrP** antibody. A mouse monoclonal antibody that binds to PTHrP amino acid sequence 1-34 and inhibits PTHrP function has been humanized to create a specific and potent agent for the treatment of patients with HHM. The mouse monoclonal antibody has been shown to have **antihypercalcemic activity** against nude mice bearing human tumors. Because a mouse antibody is highly immunogenic in human patients, the complementarity-determining regions from the mouse antibody were grafted into a human antibody. The resulting humanized antibody specifically recognizes PTHrP(1-34) and neutralizes PTHrP functions in vitro and in vivo. The humanized **anti-PTHrP** antibody was administered intravenously to HHM model animals bearing tumors such as LC-6 human lung carcinoma. These animals showed symptoms similar to those of patients with HHM (eg, hypercalcemia and cachexia). The humanized **anti-PTHrP** antibody-treated animals responded with normalization of blood ionized calcium level through an improvement of bone metabolism and calcium excretion. Moreover, the treated animals also showed an improvement in body weight, ultromotivity, metabolic alkalosis, food consumption, water intake, serum phosphorus, and renal function. Consequently, the humanized antibody-treated animals experienced complete resolution of hypercalcemia and cachexia. These results suggest that the humanized antibody would be an effective and beneficial agent for patients with HHM, and that PTHrP is a major pathogenetic factor of hypercalcemia and cachexia in patients with HHM.

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PROCESSING COMPLETED FOR L4
L13 64 DUP REMOVE L4 (136 DUPLICATES REMOVED)

=> s l13 and hyperosmolarity
L14 0 L13 AND HYPEROSMOLARITY

L15 15 L13 AND "PTHRP 1-34"

=> d l15 1-15 cbib abs

L15 ANSWER 1 OF 15 MEDLINE on STN

2003534792. PubMed ID: 14613038. Treatment of malignancy-associated hypercalcemia and cachexia with humanized anti-parathyroid hormone-related protein antibody. Sato Koh; Onuma Etsuro; Yocum Richard C; Ogata Etsuro. (Department of International Coordination, Chugai Pharmaceutical Co, Ltd, Skizuuoka, Japan.) Seminars in oncology, (2003 Oct) 30 (5 Suppl 16) 167-73. Ref: 11. Journal code: 0420432. ISSN: 0093-7754. Pub. country: United States. Language: English.

AB Parathyroid hormone-related protein (PTHrP) plays a central role in humoral hypercalcemia of malignancy (HHM), which is one of the most frequent paraneoplastic syndromes. PTHrP produced by the tumor acts through a common PTH/PTHrP receptor to promote bone resorption, inhibit calcium excretion from the kidney, and induce hypercalcemia. Patients with HHM often develop cachexia associated with typical symptoms such as anorexia, malaise, nausea, constipation, polyuria, polydipsia, and confusion. The etiology of the cachexia is not fully understood but is thought to be caused by hypercalcemia and various cytokines such as interleukin-6, tumor necrosis factor-alpha, leukemia inhibitory factor, and others. In this study, we investigated the role of PTHrP in hypercalcemia and cachexia in HHM by using humanized **anti-PTHrP** antibody. A mouse monoclonal antibody that binds to PTHrP amino acid sequence 1-34 and inhibits PTHrP function has been humanized to create a specific and potent agent for the treatment of patients with HHM. The mouse monoclonal antibody has been shown to have antihypercalcemic activity against nude mice bearing human tumors. Because a mouse antibody is highly immunogenic in human patients, the complementarity-determining regions from the mouse antibody were grafted into a human antibody. The resulting humanized antibody specifically recognizes **PTHrP(1-34)** and neutralizes PTHrP functions in vitro and in vivo. The humanized **anti-PTHrP** antibody was administered intravenously to HHM model animals bearing tumors such as LC-6 human lung carcinoma. These animals showed symptoms similar to those of patients with HHM (eg, hypercalcemia and cachexia). The humanized **anti-PTHrP** antibody-treated animals responded with normalization of blood ionized calcium level through an improvement of bone metabolism and calcium excretion. Moreover, the treated animals also showed an improvement in body weight, ultromotivity, metabolic alkalosis, food consumption, water intake, serum phosphorus, and renal function. Consequently, the humanized antibody-treated animals experienced complete resolution of hypercalcemia and cachexia. These results suggest that the humanized antibody would be an effective and beneficial agent for patients with HHM, and that PTHrP is a major pathogenetic factor of hypercalcemia and cachexia in patients with HHM.

L15 ANSWER 2 OF 15 MEDLINE on STN

2002160098. PubMed ID: 11891011. Parathyroid hormone-related protein enhances PC-3 prostate cancer cell growth via both autocrine/paracrine and intracrine pathways. Tovar Sepulveda Veronica A; Falzon Miriam. (Department of Pharmacology and Toxicology, University of Texas Medical Branch, 10th and Market Streets, Galveston, TX 77555, USA.) Regulatory peptides, (2002 May 15) 105 (2) 109-20. Journal code: 8100479. ISSN: 0167-0115. Pub. country: Netherlands. Language: English.

effects were reversed by **anti-PTHrP** antiserum. This antiserum also decreased endogenous PC-3 cell growth. Clonal PTHrP-overexpressing PC-3 cell lines also showed enhanced cell growth and [3H]thymidine incorporation and were enriched in the G2+M phase of the cell cycle, suggesting an effect of PTHrP on mitosis. Overexpression of PTHrP with the nuclear localization sequence (NLS) deletion partially reversed the growth-stimulatory effects. The growth rate of these cells was midway between that of wild-type PTHrP-overexpressing and control cells, presumably because NLS-mutated PTHrP is still secreted and acts through the cell surface PTH/PTHrP receptor. In contrast to NLS-mutated PTHrP, wild-type protein showed preferential nuclear localization. These results suggest that the proliferative effects of PTHrP in PC-3 cells are mediated via both autocrine/paracrine and intracrine pathways, and that controlling PTHrP production in prostate cancer may be therapeutically beneficial.

L15 ANSWER 3 OF 15 MEDLINE on STN

2001698964. PubMed ID: 11745216. Parathyroid hormone-related protein regulates the growth of orthotopic human lung tumors in athymic mice. Hastings R H; Burton D W; Quintana R A; Biederman E; Gujral A; Deftos L J. (Anesthesiology and Medicine Services, VA San Diego Healthcare System and the University of California, San Diego, California 92161-5085, USA.. rhhastings@ucsd.edu) . Cancer, (2001 Sep 15) 92 (6) 1402-10. Journal code: 0374236. ISSN: 0008-543X. Pub. country: United States. Language: English.

AB BACKGROUND: Parathyroid hormone-related protein (PTHrP) has growth regulatory effects for many malignant cells and may influence the progression of carcinomas of the breast, prostate, and lung. In the current study, the authors investigated the in vivo and in vitro effects of PTHrP neutralizing antibody and PTHrP treatment on the growth of BEN cells, a human lung squamous cell carcinoma line that expresses PTHrP and its receptor. METHODS: Orthotopic lung tumors were produced in 20 athymic mice with BEN-GFP cells (a clonal line that stably expresses green fluorescent protein [GFP]) by instilling suspensions of 3 x 10(6) cells per mouse into the lungs of anesthetized animals. The mice were divided into 2 groups receiving either subcutaneous mouse antihuman PTHrP antibodies or irrelevant mouse immunoglobulin (Ig) G (150 microg) twice weekly. RESULTS: After 30 days, 6 of 10 mice receiving **anti-PTHrP** antibodies had lung tumors visible on macroscopic inspection, but only 1 of the 10 mice treated with irrelevant IgG had a lung tumor that was of that size ($P < 0.01$). GFP fluorescence was significantly greater in lung homogenates of the PTHrP antibody-treated mice than in the mice treated with IgG (6006 +/- 411 vs. 2907 +/- 282 relative fluorescent units, respectively; $P < 0.001$). Although neutralizing antibodies stimulated BEN cell lung tumor growth, exogenous **PTHrP 1-34** treatment (0.01-1 nM) inhibited the growth of cultured BEN cells by approximately 40%. CONCLUSIONS: Although PTHrP expression has been reported to be associated with more aggressive malignancies, the data from the current study suggest that **PTHrP 1-34** was a paracrine growth inhibitor in BEN human lung carcinoma cells. The growth-related effects of PTHrP are complex, and can be both stimulatory and inhibitory.

L15 ANSWER 4 OF 15 MEDLINE on STN

2000056169. PubMed ID: 10588813. Parathyroid hormone-related peptide

AB [illegible] pancreatic islet. Recent data in transgenic mice suggest that PTHrP might modulate islet mass and insulin secretion. In the present study, we assessed the effect of the N-terminal PTH-like region of PTHrP on DNA synthesis in isolated rat islets. **PTHrP (1-34)**, between 1 pM and 10 nM, for 48 h stimulated []thymidine incorporation into rat islets. This effect was maximally induced, about 2.5-fold over control, by 10 pM of this peptide, decreasing thereafter. In contrast, PTHrP (38-64) amide or PTHrP (107-139) were ineffective in increasing DNA synthesis in islets. Using reverse transcription followed by PCR, we confirmed that rat islets express PTHrP and the type I PTH/PTHrP receptor. Addition of a neutralizing **anti-PTHrP** antibody to the incubation medium of proliferating islets decreased islet DNA synthesis by 30%. The effect of a submaximal dose (30 pM) of **PTHrP (1-34)** on DNA synthesis in rat islets was abolished by 25 nM bisindolylmaleimide I, a protein kinase C (PKC) inhibitor, but not by 25 microM adenosine 3',5'-cyclic monophosphorothioate, Rp-isomer, a protein kinase A inhibitor. Moreover, 100 nM phorbol-12-myristate-13-acetate for 48 h also increased DNA synthesis 2-fold over controls in islets. **PTHrP (1-34)**, at 100 nM, in contrast to 50 microM forskolin or 10 mM NaF, failed to affect adenylate cyclase activity in islet membranes. PTHrP, at 30 pM, was also found to increase 2-fold insulin released into the islet-conditioned medium within 24-48 h. Our results suggest that PTHrP is a modulator of pancreatic islet growth and/or function by a PKC-mediated mechanism.

L15 ANSWER 5 OF 15 MEDLINE on STN

97329817. PubMed ID: 9186276. Parathyroid hormone-related protein in neonatal and reproductive goats determined by a sensitive time-resolved immunofluorometric assay. Rong H; Hydbring E; Olsson K; Burtis W J; Rankin W; Grill V; Bucht E. (Department of Molecular Medicine, Karolinska Hospital and Institute, Stockholn, Sweden.) European journal of endocrinology / European Federation of Endocrine Societies, (1997 May) 136 (5) 546-51. Journal code: 9423848. ISSN: 0804-4643. Pub. country: ENGLAND: United Kingdom. Language: English.

AB OBJECTIVE: High concentrations of parathyroid hormone-related protein (PTHrP) have been found in goat milk but it is not known whether it can enter the circulation of the neonate. In this study we have developed a sensitive two-site lanthanide immunofluorometric assay (IFMA) using dissociation and enhancement time-resolved fluorometry to address this question. METHOD: Affinity-purified **anti-PTHrP** 38-67 raised in rabbit was biotinylated and immobilized in streptavidin-coated microtitration wells as a 'capture' antibody. As a signal, affinity-purified **anti-PTHrP 1-34**, raised in sheep, was labeled with an europium chelate. A sensitivity of 0.3 pmol/l was achieved. PTHrP levels were determined in the plasma of eleven neonatal, seven parturient and six non-pregnant, non-lactating goats as well as in goat milk. RESULTS: The circulating PTHrP levels (mean +/- S.D.) were significantly increased at day 1 (6.1 +/- 1.7 pmol/l: $P < 0.01$) and day 3 (3.5 +/- 0.6 pmol/l: $P < 0.05$) after birth in the male kids (n = 8) bottle-fed with milk from the dams, compared with before (2.2 +/- 0.7 pmol/l) and 30 min after (2.0 +/- 0.6 pmol/l) the first feeding and 14 days (2.4 +/- 0.8 pmol/l) later. In the female kids (n = 3) fed with formula there was no such increase and the concentrations remained between 1.6-1.9 pmol/l. In the parturient goats the mean +/- S.D. PTHrP levels before, during and after parturition were 2.9 +/- 1.7, 4.2 +/- 2.4 and 3.7 +/- 2.2 pmol/l respectively (n = 7) which demonstrated that plasma

L15 ANSWER 6 OF 15 MEDLINE on STN

96295015. PubMed ID: 8726463. Parathyroid hormone-related protein is induced during lethal endotoxemia and contributes to endotoxin-induced mortality in rodents. Funk J L; Moser A H; Strewler G J; Feingold K R; Grunfeld C. (Department of Medicine, University of California, San Francisco, USA.) Molecular medicine (Cambridge, Mass.), (1996 Mar) 2 (2) 204-10. Journal code: 9501023. ISSN: 1076-1551. Pub. country: United States. Language: English.

AB BACKGROUND: Parathyroid hormone-related protein (PTHrP) is a ubiquitous and highly conserved vasoactive peptide whose role and regulation in normal physiology remain an enigma. Recently, we demonstrated that low-dose endotoxin (LPS) induces intrasplenic, but not systemic, levels of PTHrP; and that tumor necrosis factor, a pro-inflammatory cytokine, is the major mediator of this effect. We have therefore hypothesized that, with higher, lethal doses of endotoxin, PTHrP could be induced in multiple tissues to such a degree that it could contribute to the lethality of septic shock. MATERIALS AND METHODS: Northern blot analysis was used to measure PTHrP mRNA levels in vital organs of rats after administration of a near lethal dose (5 mg/250 g) of LPS (or vehicle alone). Plasma levels of PTHrP were also measured by immunoradiometric assay. The ability of the immunoglobulin fraction of two different **PTHrP**(**1-34**) antisera to protect from LPS-induced lethality was also studied in mice using survival analysis. RESULTS: In response to a near-lethal dose of endotoxin, PTHrP mRNA levels increased acutely in every vital organ examined (spleen, lung, heart, kidney, and liver). Circulating levels of PTHrP also increased, peaking 2 hr after administration of high-dose endotoxin. Passive immunization of mice with **anti-PTHrP**(**1-34**) antibody 6 hr prior to administration of a lethal dose of LPS protected mice from endotoxin-induced death ($p < 0.00005$). CONCLUSIONS: These results suggest that PTHrP belongs to the cascade of pro-inflammatory cytokines induced during lethal endotoxemia that is responsible for the toxic effects of LPS.

L15 ANSWER 7 OF 15 MEDLINE on STN

94073918. PubMed ID: 8252579. Parathyroid hormone related peptide gene expression in human fetal and adult heart. Bui T D; Shallal A; Malik A N; al-Mahdawi S; Moscoso G; Bailey M E; Burton P B; Moniz C. (King's College Hospital, London, United Kingdom.) Cardiovascular research, (1993 Jul) 27 (7) 1204-8. Journal code: 0077427. ISSN: 0008-6363. Pub. country: ENGLAND: United Kingdom. Language: English.

AB OBJECTIVE: The aim was to investigate the expression of parathyroid hormone related peptide (PTHrP) gene in the human fetal and adult heart. METHODS: Molecular biological techniques were employed as well as immunocytochemistry and western blot analysis using rabbit polyclonal **anti-PTHrP**(**1-34**) and **anti-PTHrP** (56-86) on normal human fetal and adult heart tissues. Northern blot analysis of both normal human fetal and adult heart total RNA, using a human full length cDNA probe, and polymerase chain reaction analysis of normal human fetal and adult heart cDNAs with exon specific oligonucleotides were carried out. RESULTS: Positive staining was detected with both **anti-PTHrP**(**1-34**) and **anti-PTHrP**(56-86) in fetal heart at 12 weeks of gestation. In both fetal and adult hearts, multiple putative PTHrP proteins were observed with apparent molecular mass of 14-125 kDa.

cardiovascular system.

L15 ANSWER 8 OF 15 MEDLINE on STN
93355917. PubMed ID: 8352067. Passive immunization with anti-parathyroid hormone-related protein monoclonal antibody markedly prolongs survival time of hypercalcemic nude mice bearing transplanted human PTHrP-producing tumors. Sato K; Yamakawa Y; Shizume K; Satoh T; Nohtomi K; Demura H; Akatsu T; Nagata N; Kasahara T; Ohkawa H; +. (Institute of Clinical Endocrinology, Tokyo Women's Medical College, Japan.) Journal of bone and mineral research : official journal of the American Society for Bone and Mineral Research, (1993 Jul) 8 (7) 849-60. Journal code: 8610640. ISSN: 0884-0431. Pub. country: United States. Language: English.
AB Malignancy-associated hypercalcemia is mainly caused by excessive production of parathyroid hormone-related protein (PTHrP) by the tumor. Using **anti-PTHrP-(1-34)** monoclonal murine antibody (**anti-PTHrP** MoAb), we studied whether repeated injection of the homologous antibody would continuously decrease the serum calcium concentration in hypercalcemic nude mice bearing transplanted human PTHrP-producing tumors, leading to prolongation of their survival time. Daily SC injections of **anti-PTHrP** MoAb decreased the serum calcium concentration almost to within the normal range in nude mice bearing transplanted human PTHrP-producing tumors (T3M-1, EC-GI, PC-3, and FA-6) but not in a nude mouse bearing a transplanted parathyroid carcinoma. The antibody did not affect FA-6 tumor growth either in vitro or in vivo. Pancreatic carcinoma cells (FA-6), which caused the most severe hypercalcemia, were inoculated into 6-week-old nude mice. When severe hypercalcemia (approximately 19 mg/dl) had developed, daily SC injection of **anti-PTHrP** MoAb was started. Within 18 days of this time point, all untreated tumor-bearing mice (n = 10) died of hypercalcemia and cachexia, whereas all the treated mice (n = 10) showed an increase in body weight and survived for at least 25 days. Histologic examination of the treated mice revealed a marked decrease in osteoclastic bone resorption, without toxicologic findings in the kidney and liver. These results suggest that passive immunization against PTHrP can continuously ameliorate the hypercalcemia and markedly prolong the survival time of severely hypercalcemic, tumor-bearing mice. If a human monoclonal antibody against **PTHrP-(1-34)** could be developed, then passive immunization would be potentially one of the most effective therapies for patients with malignancy-associated hypercalcemia due to excessive production of PTHrP.

L15 ANSWER 9 OF 15 MEDLINE on STN
92037384. PubMed ID: 1657580. Suckling-mediated increases in urinary phosphate and 3',5'-cyclic adenosine monophosphate excretion in lactating rats: possible systemic effects of parathyroid hormone-related protein. Yamamoto M; Duong L T; Fisher J E; Thiede M A; Caulfield M P; Rosenblatt M. (Merck Sharp and Dohme Research Laboratories, West Point, Pennsylvania 19486.) Endocrinology, (1991 Nov) 129 (5) 2614-22. Journal code: 0375040. ISSN: 0013-7227. Pub. country: United States. Language: English.
AB Earlier studies have shown that lactation-induced bone loss in the rat is both PTH- and vitamin D-independent and have suggested the involvement of another, as yet unidentified, factor(s) in the altered calcium metabolism which accompanies lactation. In the present study, we investigated the possibility that PTH-related protein (PTHrP), which is produced in lactating mammary glands, is a putative calciotropic factor acting systemically during lactation. To test this hypothesis, we examined

were not abolished by thyroparathyroidectomy, hence they are not attributable to a transient increase in PTH secretion. Administration of PRL or oxytocin did not induce significant P-uria. When lactating rats were pretreated with **anti-PTHrP** anti-serum, the suckling-associated P-uria was prolonged and augmented. This prolongation of P-uria was similar to the effects observed when exogenous **PTHrP (1-34)**amide was administered in the presence of the antiserum. These data support the hypothesis that some of the PTHrP produced in lactating mammary glands may be released systemically during suckling and act in an endocrine manner on target organs such as the kidney.

L15 ANSWER 10 OF 15 MEDLINE on STN

90317697. PubMed ID: 2196348. Immunohistochemical localization of parathyroid hormone-related protein in parathyroid adenoma and hyperplasia. Danks J A; Ebeling P R; Hayman J A; Diefenbach-Jagger H; Collier F M; Grill V; Southby J; Moseley J M; Chou S T; Martin T J. (St Vincent's Institute of Medical Research, St Vincent's Hospital, Melbourne, Australia.) Journal of pathology, (1990 May) 161 (1) 27-33. Journal code: 0204634. ISSN: 0022-3417. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Parathyroid hormone-related protein (PTHrP) is invoked as the cause of humoral hypercalcaemia of malignancy (HHM); it is contained in the keratinocyte layer of normal skin; and there is evidence that is is produced by fetal parathyroids. Antibodies against synthetic PTHrP peptides have been raised in rabbits and sheep. This immunohistochemical study has found that primary parathyroid adenomata and hyperplastic glands from patients with chronic renal failure stain positively with antisera against **PTHrP(1-34)** and PTHrP(50-69). Primary hyperplastic glands are negative. No staining with **anti -PTHrP**(106-141) antiserum could be detected immunohistochemically in any of the parathyroid adenomata or hyperplasia.

L15 ANSWER 11 OF 15 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN

2003:258594 Document No.: PREV200300258594. Parathyroid hormone-related protein regulates lung phospholipids through effects on type II cell proliferation in silica lung injury. Hastings, Randolph H. [Reprint Author]; Quintana, Rick; Rascon, Yvette; Duey, Devin; Burton, Douglas W.; Deftos, Leonard J.. Anesthesiology, VA San Diego Healthcare System, 3350 La Jolla Village Dr. (125), San Diego, CA, 92161, USA. rhhastings@ucsd.edu; rquintan71@hotmail.com; yvetter3@hotmail.com; dduey@ucsd.edu; dwburton@ucsd.edu; ljdeftos@ucsd.edu. FASEB Journal, (March 2003) Vol. 17, No. 4-5, pp. Abstract No. 562.2. http://www.fasebj.org/. e-file. Meeting Info.: FASEB Meeting on Experimental Biology: Translating the Genome. San Diego, CA, USA. April 11-15, 2003. FASEB. ISSN: 0892-6638 (ISSN print). Language: English.

AB Lung levels of parathyroid hormone-related protein (PTHrP), an alveolar type II cell growth inhibitor, rise concurrent with the alveolar phospholipidosis characteristic of silica lung injury. PTHrP could alternatively augment phospholipidosis since **PTHrP 1-34** and 67-86 are secretagogues, or limit phospholipid production by inhibiting type II cell growth. This study's purpose was to assess phospholipids and type II cell growth in silica injury after reducing lung PTHrP. Silica-injured rats received intratracheal 75 mug 1A5, a neutralizing **anti-PTHrP 1-34** antibody, 8A4, an isotype control, or 1A5 plus 15 mug PTHrP 67-86, plus

0.05). PCNA-positive cells were 17 (7, 30) cells/200 high power [illegible]
[median (interquartile gap)], 210 (138, 267) and 17 (15, 31) for 8A4, 1A5, and 1A5 + PTHrP groups, respectively. In summary, neutralizing PTHrP antibodies augment type II cell proliferation and increase PL after silica injury. Thus, endogenous PTHrP may act to limit phospholipidosis and type II cell growth.

L15 ANSWER 12 OF 15 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
91:602394 The Genuine Article (R) Number: GM349. SUCKLING-MEDIATED INCREASES IN URINARY PHOSPHATE AND 3',5'-CYCLIC ADENOSINE-MONOPHOSPHATE EXCRETION IN LACTATING RATS - POSSIBLE SYSTEMIC EFFECTS OF PARATHYROID HORMONE-RELATED PROTEIN. YAMAMOTO M (Reprint); DUONG L T; FISHER J E; THIEDE M A; CAULFIELD M P; ROSENBLATT M. MERCK SHARP & DOHME LTD, W26-207, W POINT, PA, 19486 (Reprint). ENDOCRINOLOGY (1991) Vol. 129, No. 5, pp. 2614-2622. Pub. country: USA. Language: ENGLISH.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB Earlier studies have shown that lactation-induced bone loss in the rat is both PTH- and vitamin D-independent and have suggested the involvement of another, as yet unidentified, factor(s) in the altered calcium metabolism which accompanies lactation. In the present study, we investigated the possibility that PTH-related protein (PTHrP), which is produced in lactating mammary glands, is a putative calciotropic factor acting systemically during lactation. To test this hypothesis, we examined changes in urinary phosphate and cAMP excretion in relation to suckling since phosphaturia (P-uria) and increased urinary cAMP excretion are sensitive parameters of PTHrP action on the kidney. When lactating rats (separated from their pups overnight) were allowed to suckle pups for 1 h, they showed a marked P-uria which lasted 3-4 h. In most instances, a transient increase in cAMP excretion preceded the P-uria. These effects were not abolished by thyroparathyriodectomy; hence they are not attributable to a transient increase in PTH secretion. Administration of PRL or oxytocin did not induce significant P-uria. When lactating rats were pretreated with **anti-PTHrP** anti-serum, the suckling-associated P-uria was prolonged and augmented. This prolongation of P-uria was similar to the effects observed when exogenous **PTHrP** (**1-34**)amide was administered in the presence of the antiserum. These data support the hypothesis that some of the PTHrP produced in lactating mammary glands may be released systemically during suckling and act in an endocrine manner on target organs such as the kidney.

L15 ANSWER 13 OF 15 CAPLUS COPYRIGHT 2004 ACS on STN
2002:142542 Document No. 136:194679 PTHrP agonists and antagonists as vascular relaxation agents and inhibitors. Ohhashi, Toshio (Chugai Seiyaku Kabushiki Kaisha, Japan). PCT Int. Appl. WO 2002013852 A1 20020221, 44 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (Japanese). CODEN: PIXXD2. APPLICATION: WO 2001-JP6943 20010810. PRIORITY: JP 2000-243873 20000811.
AB It is intended to provide vascular relaxation agents and vascular relaxation inhibitors. Namely, vascular relaxation agents containing PTHrP or its fragment; and vascular relaxation inhibitors containing a substance

organ failure, and others.

L15 ANSWER 14 OF 15 CAPLUS COPYRIGHT 2004 ACS on STN
2001:31355 Document No. 134:99582 Remedies for drug-resistant hypercalcemia. Saito, Hidemi; Tsunenari, Toshiaki; Onuma, Etsuro (Chugai Seiyaku Kabushiki Kaisha, Japan). PCT Int. Appl. WO 2001002012 A1 20010111, 118 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (Japanese). CODEN: PIXXD2. APPLICATION: WO 2000-JP4523 20000706. PRIORITY: JP 1999-192270 19990706.
AB Remedies for drug-resistant hypercalcemia which contain as the active ingredient a substance inhibiting the binding of a parathyroid hormone-related peptide to its receptor. Therapeutics for drug-resistant hypercalcemia include bone resorption inhibitor (e.g. bisphosphates and/or calcitonin), calcium excretion promoter, intestinal calcium absorption inhibitor, or loop diuretic. The PTHrP and receptor-binding inhibitors are PTHrP receptor antagonist such as **anti-PTHrP** antibodies or fragments or chimeric antibodies.

L15 ANSWER 15 OF 15 CAPLUS COPYRIGHT 2004 ACS on STN
1993:226595 Document No. 118:226595 Determination of parathormone-related protein by sandwich immunoassay. Kasahara, Hiroyuki; Tanaka, Shuichi; Horikawa, Hideji (Daiich Radioisotope Laboratories, Ltd., Japan). Jpn. Kokai Tokkyo Koho JP 04364463 A2 19921216 Heisei, 12 pp. (Japanese). CODEN: JKXXAF. APPLICATION: JP 1991-166242 19910612.
AB Parathormone-related protein (PTHrP) is determined by sandwich immunoassay using an antibody recognizing the amino terminus of PTHrP and a 2nd antibody recognizing the middle region of PTHrP (to form a 1st antibody-test antigen-2nd antibody complex for PTHrP determination). Thus, PTHrP was determined by RIA using an **anti-PTHrP** (**1-34**) antibody-sensitized bead and I125-labeled **anti-PTHrP** (109-141). The method was accurate and simple.

=> s PTHrP receptor antagonist
L16 112 PTHRP RECEPTOR ANTAGONIST

=> s l16 and binding
L17 22 L16 AND BINDING

=> s l17 and antibody
L18 6 L17 AND ANTIBODY

=> dup remove l18
PROCESSING COMPLETED FOR L18
L19 6 DUP REMOVE L18 (0 DUPLICATES REMOVED)

=> d l19 1-6 cbib abs

L19 ANSWER 1 OF 6 CAPLUS COPYRIGHT 2004 ACS on STN
2002:888597 Document No. 138:3671 Angiogenesis inhibitors that block

TT, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (Japanese). CODEN: PIXXD2. APPLICATION: WO 2002-JP4586 20020510. PRIORITY: JP 2001-140659 20010510.

AB It is found out that angiogenesis can be inhibited by a substance which inhibits the **binding** of a parathyroid hormone-associated peptide (e.g. PTHrP) to its receptor. The angiogenesis inhibitors can be anti-PTHrP **antibodies**, **antibody** fragments, humanized or chimeric **antibodies**, PTH receptor antagonists, or antisense oligonucleotides specific to PTHrP. These modified anti-PTHrP **antibodies** and PTH receptor antagonists are useful as antitumor agents and bone metastasis inhibitors.

L19 ANSWER 2 OF 6 CAPLUS COPYRIGHT 2004 ACS on STN

2002:142542 Document No. 136:194679 PTHrP agonists and antagonists as vascular relaxation agents and inhibitors. Ohhashi, Toshio (Chugai Seiyaku Kabushiki Kaisha, Japan). PCT Int. Appl. WO 2002013852 A1 20020221, 44 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (Japanese). CODEN: PIXXD2. APPLICATION: WO 2001-JP6943 20010810. PRIORITY: JP 2000-243873 20000811.

AB It is intended to provide vascular relaxation agents and vascular relaxation inhibitors. Namely, vascular relaxation agents containing PTHrP or its fragment; and vascular relaxation inhibitors containing a substance inhibiting the **binding** of PTHrP to its receptor. PTHrPs and fragments are vascular relaxation agent and are useful for treating vasoconstriction-related diseases such as myocardial infarction, hypertension, thrombosis, and angina. PTHrP/**PTHrP receptor antagonists** and **antibodies** are vascular relaxation inhibitors and are useful for treating vasodilation-related diseases such as hypotension, terminal circulation insufficiency, multiple organ failure, and others.

L19 ANSWER 3 OF 6 CAPLUS COPYRIGHT 2004 ACS on STN

2001:661283 Document No. 135:240920 Tissue decomposition inhibitor. Saito, Hidemi; Tsunenari, Toshiaki; Onuma, Etsuro; Sato, Koh (Chugai Seiyaku K. K., Japan). PCT Int. Appl. WO 2001064249 A1 20010907, 131 pp. DESIGNATED STATES: W: CA, JP, US. (Japanese). CODEN: PIXXD2. APPLICATION: WO 2000-JP5886 20000830. PRIORITY: JP 2000-52414 20000228.

AB A tissue decomposition inhibitor which contains a substance inhibiting the **binding** of a parathyroid hormone-associated peptide to its receptor. The tissue decomposition inhibitor is a **PTHrP receptor antagonist** such as **antibody**, chimeric **antibody**, monoclonal **antibody**, or **antibody** fragment specifically binds to PTHrP receptor. The **PTHrP receptor antagonist** is useful for inhibiting decomposition muscle or adipose tissue and elevation of inflammatory cytokine. The **PTHrP receptor antagonist** is therefore useful for treating sepsis, trauma, muscle dystrophy, cancer-associated weight loss,.

PIXXD2. APPLICATION: WO 2000 [illegible] 20000125.

AB Remedies or preventives for dental diseases which contain as the active ingredient a substance inhibiting the **binding** of a parathyroid hormone-associated peptide to its receptor. The **PTHrP receptor antagonists** are **antibodies**, monoclonal **antibodies**, humanized or chimeric **antibodies**, or their fragments.

L19 ANSWER 5 OF 6 CAPLUS COPYRIGHT 2004 ACS on STN

2001:31355 Document No. 134:99582 Remedies for drug-resistant hypercalcemia. Saito, Hidemi; Tsunenari, Toshiaki; Onuma, Etsuro (Chugai Seiyaku Kabushiki Kaisha, Japan). PCT Int. Appl. WO 2001002012 A1 20010111, 118 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (Japanese). CODEN: PIXXD2. APPLICATION: WO 2000-JP4523 20000706. PRIORITY: JP 1999-192270 19990706.

AB Remedies for drug-resistant hypercalcemia which contain as the active ingredient a substance inhibiting the **binding** of a parathyroid hormone-related peptide to its receptor. Therapeutics for drug-resistant hypercalcemia include bone resorption inhibitor (e.g. bisphosphates and/or calcitonin), calcium excretion promoter, intestinal calcium absorption inhibitor, or loop diuretic. The PTHrP and receptor-**binding** inhibitors are **PTHrP receptor antagonist** such as anti-PTHrP **antibodies** or fragments or chimeric **antibodies**.

L19 ANSWER 6 OF 6 CAPLUS COPYRIGHT 2004 ACS on STN

1998:764302 Document No. 130:10622 **Antibody** to parathyroid hormone-related peptide (PTHrP) or the **PTHrP receptor antagonist** as a cancerous cachexia remedy. Sato, Koh; Tunenari, Toshiaki; Ishii, Kimie (Chugai Seiyaku Kabushiki Kaisha, Japan). PCT Int. Appl. WO 9851329 A1 19981119, 125 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (Japanese). CODEN: PIXXD2. APPLICATION: WO 1998-JP2116 19980513. PRIORITY: JP 1997-125505 19970515; JP 1997-194445 19970718.

AB Disclosed is a cancerous cachexia remedy comprising a substance inhibiting the **binding** of a parathyroid hormone-related peptide (PTHrP) and its receptor, which inhibitor may consist of an antagonist against the receptor or an **antibody** to the PTHrP. Anti-cachexia effects of humanized mouse monoclonal **antibody** 23-57-137-1 were observed by using the nude mice transplanted with OCC-1 human buccal cancer cell, which effects were based on the blood level of Ca, body weight, and survival.

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regulation of intrauterine PTHrP, PTH/PTHrP receptor ... SHR fetal weight. Wlodek M E; Di Nicolantonio R; Westcott K T; Farrugia W; Ho P W M; Moseley J M. (Department of Physiology, The University of Melbourne, Grattan Street, Carlton,Victoria, Australia 3010.. m.wlodek@unimelb.edu.au) . Placenta, (2004 Jan) 25 (1) 53-61. Journal code: 8006349. ISSN: 0143-4004. Pub. country: England: United Kingdom. Language: English.

AB Parathyroid hormone-related protein (PTHrP) has important roles in fetal growth and development through stimulation of placental calcium transport, vasodilatation of the uteroplacental vasculature and regulation of cellular growth and differentiation. The growth restricted spontaneously hypertensive rat (SHR) has reduced fetal plasma, placental and amniotic fluid PTHrP concentrations compared to its progenitor, the Wistar Kyoto (WKY) rat. The aim of this study was to determine whether intrauterine PTHrP infusions can restore PTHrP levels and promote SHR fetal growth. PTHrP(1-34), midmolecule PTHrP(67-94), the PTH/**PTHrP receptor antagonist** [Asn(10), Leu(11)]-PTHrP(7-34) or vehicle were infused via a mini-osmotic pump between 10 and 20 days of gestation into the uterine lumen of SHR and WKY rats. Uterine, placental, amniotic fluid and plasma (fetal and maternal) PTHrP were measured via N-terminal radioimmunoassay. PTH/PTHrP receptor antagonism and mid-molecule PTHrP(67-94) induced endogenous intrauterine PTHrP production with receptor antagonism eliciting a greater and more wide spread effect. The PTH/**PTHrP receptor antagonist** [Asn(10), Leu(11)]-PTHrP(7-34) acting through a receptor other than the PTH/PTHrP receptor increased SHR fetal and placental weights above vehicle ($P<0.05$) to that of the WKY and restored SHR amniotic fluid volume ($P<0.05$). This was associated with a highly significant up regulation of placental, uterine and plasma (fetal and maternal) PTHrP ($P<0.05$). Modest increases in placental and uterine PTHrP ($P<0.05$) following intrauterine infusions of PTHrP(1-34) and PTHrP(67-94) had no effect on WKY and SHR fetal weight. Effective growth promoting actions of increased endogenous PTHrP were observed following PTH/PTHrP receptor antagonism rather than exogenous PTHrP administration. A novel finding was that mid-molecule PTHrP also up regulates endogenous intrauterine N-terminal PTHrP production supporting the existence of a mid-molecule receptor. This study highlights that an increase in endogenous uterine, placental and fetal plasma PTHrP following PTH/PTHrP receptor antagonism was associated with increased SHR fetal growth presumably by improving placental growth and function.

L20 ANSWER 2 OF 32 MEDLINE on STN DUPLICATE 2

2003156120. PubMed ID: 12674335. Functional type I PTH/PTHrP receptor in freshly isolated newborn rat keratinocytes: identification by RT-PCR and immunohistochemistry. Errazahi Amina; Bouizar Zhor; Lieberherr Michele; Souil Evelyne; Rizk-Rabin Marthe. (Centre National de la Recherche Scientifique, CNRS UMR 8104--INSERM U.567 Equipe Endocrinologie, Os et Developpement, Hopital Saint Vincent de Paul, Paris and Jouy-en-Josas, France.) Journal of bone and mineral research : official journal of the American Society for Bone and Mineral Research, (2003 Apr) 18 (4) 737-50. Journal code: 8610640. ISSN: 0884-0431. Pub. country: United States. Language: English.

AB The presence of identical or distinct type I parathyroid hormone (PTH)/parathyroid hormone-related peptide (PTHrP) receptors in keratinocytes is still a matter of debate. We studied the expression and functionality of PTHrP receptors in freshly isolated keratinocytes from newborn rat skin. Four overlapping primers, amplifying different regions in the rat PTH receptor, were used for reverse transcriptase-polymerase

keratinocyte RNA were identical to those from kidney [illegible] The cloned four transcripts showed 100% of homologies with the cDNA sequence from bone ROS cells. Keratinocytes, freshly isolated or present in situ in the epidermis, recognized an anti-PTH receptor antibody (PTH-II) directed against the receptor extracellular domain. Western blotting showed the same protein patterns in keratinocytes, kidney, and ROS cell extracts. Low doses of PTHrP(1-34) (10(-12)-10(-9) M) increased the cell number studied by [3H]thymidine incorporation and DNA content. Treatment with the PTH/**PTHrP receptor antagonist** [Asn10, Leu11, D Trp12] PTHrP(7-34) or two different PTH receptor antibodies inhibited the increase in cell proliferation induced by PTHrP(1-34). All these findings indicate that newborn rat epidermis and keratinocytes express functional PTHrP receptors, which are identical to type I PTH/PTHrP receptor and are recognized by PTHrP(1-34).

L20 ANSWER 3 OF 32 MEDLINE on STN DUPLICATE 3

2003442272. PubMed ID: 12928013. Relaxant effects of parathyroid hormone and parathyroid hormone-related peptides on oviduct motility in birds and mammals: possible role of nitric oxide. Francis M; Arkle M; Martin L; Butler T M; Cruz M C; Opare-Aryee G; Dacke C G; Brown J F. (Division of Pharmacology, University of Portsmouth, St. Michael's Building, White Swan Road, Portsmouth PO1 2DT, UK.) General and comparative endocrinology, (2003 Sep) 133 (2) 243-51. Journal code: 0370735. ISSN: 0016-6480. Pub. country: United States. Language: English.

AB Parathyroid hormone (PTH) and PTH-related peptides (PTHrP) have previously been shown to modulate the contractile state of numerous types of smooth muscle. The effects of N-terminal PTH and PTHrP on spontaneous in vitro contractility of oviducal smooth muscle using tissues from egg-laying Japanese quail (10-15 h post ovulation), 4 and 9 days pregnant mouse uterus were investigated. Myometrial tissues from both species contracted vigorously for several hours, when incubated in organ baths in De Jalon's solution gassed with 5%CO2/95%O2. Contractions were enhanced in high (1.2-2.5 mM) compared with low (0.1-0.5 mM) calcium (Ca) containing media. Bovine PTH(1-34) (bPTH(1-34)), human PTH(1-34 amide) (hPTHrP(1-34) amide), and hPTHrP(1-40) caused similar concentration-related inhibition of contractions in media containing 1.2mM Ca over a range of 10(-9) to 10(-7)M, whereas C-terminal hPTHrP(107-139) was devoid of such activity. Responses to bPTH(1-34) in 4 and 9-day pregnant mouse tissues were similar but hPTHrP(1-40) showed substantial loss of activity in 9-day, compared with 4-day pregnant mouse tissues. Repeated exposure of mouse uterine tissue to the peptides resulted in desensitisation of responses. The EC50 responses of mouse tissues were inhibited by the PTH/**PTHrP receptor antagonist**, hPTHrP(7-34) amide. Responses to bPTH(1-34) were also inhibited by both non-selective and selective neuronal nitric oxide synthase (NOS) inhibitors N(omega)-nitro-L-arginine methyl ester (0.01-1mM) and 7-nitroindazole (0.01-10 microM), respectively. Both NOS inhibitors were more effective in inhibiting bPTH(1-34)-induced relaxation in the absence of L-arginine compared with in the presence of 1mM L-arginine (a NOS substrate) in the incubation media. It is concluded that relaxant responses to N-terminal PTH and PTHrP peptides are well conserved in oviducal and uterine tissues from avian and mammalian species. The results also suggest that NO may be responsible for mediating relaxant activities of these peptides in pregnant mouse uterine tissue.

L20 ANSWER 4 OF 32 CAPLUS COPYRIGHT 2004 ACS on STN

2002:888597 Document No. 138:3671 Angiogenesis inhibitors that block binding

RE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM,
TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ,
MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES,
FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG,
TR. (Japanese). CODEN: PIXXD2. APPLICATION: WO 2002-JP4586 20020510.
PRIORITY: JP 2001-140659 20010510.

AB It is found out that angiogenesis can be inhibited by a substance which inhibits the binding of a parathyroid hormone-associated peptide (e.g. PTHrP) to its receptor. The angiogenesis inhibitors can be anti-PTHrP antibodies, antibody fragments, humanized or chimeric antibodies, PTH receptor antagonists, or antisense oligonucleotides specific to PTHrP. These modified anti-PTHrP antibodies and PTH receptor antagonists are useful as antitumor agents and bone metastasis inhibitors.

L20 ANSWER 5 OF 32 CAPLUS COPYRIGHT 2004 ACS on STN

2002:142542 Document No. 136:194679 PTHrP agonists and antagonists as vascular relaxation agents and inhibitors. Ohhashi, Toshio (Chugai Seiyaku Kabushiki Kaisha, Japan). PCT Int. Appl. WO 2002013852 A1 20020221, 44 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (Japanese). CODEN: PIXXD2. APPLICATION: WO 2001-JP6943 20010810. PRIORITY: JP 2000-243873 20000811.

AB It is intended to provide vascular relaxation agents and vascular relaxation inhibitors. Namely, vascular relaxation agents containing PTHrP or its fragment; and vascular relaxation inhibitors containing a substance inhibiting the binding of PTHrP to its receptor. PTHrPs and fragments are vascular relaxation agent and are useful for treating vasoconstriction-related diseases such as myocardial infarction, hypertension, thrombosis, and angina. PTHrP/**PTHrP receptor antagonists** and antibodies are vascular relaxation inhibitors and are useful for treating vasodilation-related diseases such as hypotension, terminal circulation insufficiency, multiple organ failure, and others.

L20 ANSWER 6 OF 32 MEDLINE on STN DUPLICATE 4

2002124740. PubMed ID: 11839533. Leptin mediates the parathyroid hormone-related protein paracrine stimulation of fetal lung maturation. Torday J S; Sun H; Wang L; Torres E; Sunday M E; Rubin L P. (Department of Pediatrics and Obstetrics and Gynecology, Harbor-University of California Los Angeles Research and Education Institute, Torrance, California 90502, USA.. jtorday@prl.humc.edu) . American journal of physiology. Lung cellular and molecular physiology, (2002 Mar) 282 (3) L405-10. Journal code: 100901229. ISSN: 1040-0605. Pub. country: United States. Language: English.

AB Developing rat lung lipofibroblasts express leptin beginning on embryonic day (E) 17, increasing 7- to 10-fold by E20. Leptin and its receptor are expressed mutually exclusively by fetal lung fibroblasts and type II cells, suggesting a paracrine signaling "loop." This hypothesized mechanism is supported by the following experimental data: 1) leptin stimulates the de novo synthesis of surfactant phospholipid by both fetal rat type II cells (400% x 100 ng(-1) x ml(-1) x 24 h(-1)) and adult human airway epithelial cells (85% x 100 ng(-1) x 24 h(-1)); 2) leptin is

protein B (SP-B; >25-101d/24 h) by fetal rat lung explants, an effect that is blocked by a leptin antibody; and 5) a **PTHrP receptor antagonist** inhibits the expression of leptin mRNA by explants but does not inhibit leptin stimulation of surfactant phospholipid or SP-B expression, indicating that PTHrP paracrine stimulation of type II cell maturation requires leptin expression by lipofibroblasts. This is the first demonstration of a paracrine loop that functionally cooperates to induce alveolar acinar lung development.

L20 ANSWER 7 OF 32 CAPLUS COPYRIGHT 2004 ACS on STN
2001:661283 Document No. 135:240920 Tissue decomposition inhibitor. Saito, Hidemi; Tsunenari, Toshiaki; Onuma, Etsuro; Sato, Koh (Chugai Seiyaku K. K., Japan). PCT Int. Appl. WO 2001064249 A1 20010907, 131 pp. DESIGNATED STATES: W: CA, JP, US. (Japanese). CODEN: PIXXD2. APPLICATION: WO 2000-JP5886 20000830. PRIORITY: JP 2000-52414 20000228.
AB A tissue decomposition inhibitor which contains a substance inhibiting the binding of a parathyroid hormone-associated peptide to its receptor. The tissue decomposition inhibitor is a **PTHrP receptor antagonist** such as antibody, chimeric antibody, monoclonal antibody, or antibody fragment specifically binds to PTHrP receptor. The **PTHrP receptor antagonist** is useful for inhibiting decomposition muscle or adipose tissue and elevation of inflammatory cytokine. The **PTHrP receptor antagonist** is therefore useful for treating sepsis, trauma, muscle dystrophy, cancer-associated weight loss,.

L20 ANSWER 8 OF 32 CAPLUS COPYRIGHT 2004 ACS on STN
2001:564867 Document No. 135:166015 Remedies and preventives for dental diseases. Kato, Atsuhiko; Suzuki, Masami; Sugimoto, Tetsuro (Chugai Seiyaku Kabushiki Kaisha, Japan). PCT Int. Appl. WO 2001054725 A1 20010802, 135 pp. DESIGNATED STATES: W: JP, US. (Japanese). CODEN: PIXXD2. APPLICATION: WO 2000-JP8875 20001214. PRIORITY: JP 2000-83034 20000125.
AB Remedies or preventives for dental diseases which contain as the active ingredient a substance inhibiting the binding of a parathyroid hormone-associated peptide to its receptor. The **PTHrP receptor antagonists** are antibodies, monoclonal antibodies, humanized or chimeric antibodies, or their fragments.

L20 ANSWER 9 OF 32 CAPLUS COPYRIGHT 2004 ACS on STN
2001:31355 Document No. 134:99582 Remedies for drug-resistant hypercalcemia. Saito, Hidemi; Tsunenari, Toshiaki; Onuma, Etsuro (Chugai Seiyaku Kabushiki Kaisha, Japan). PCT Int. Appl. WO 2001002012 A1 20010111, 118 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (Japanese). CODEN: PIXXD2. APPLICATION: WO 2000-JP4523 20000706. PRIORITY: JP 1999-192270 19990706.
AB Remedies for drug-resistant hypercalcemia which contain as the active ingredient a substance inhibiting the binding of a parathyroid hormone-related peptide to its receptor. Therapeutics for drug-resistant hypercalcemia include bone resorption inhibitor (e.g. bisphosphates and/or calcitonin), calcium excretion promoter, intestinal calcium absorption

hormone-related protein in cultured podocyte...
W; Endlich K. (Institute of Anatomy and Cell Biology, University of Heidelberg, Germany.. karlhans.endlich@urz.uni-heidelberg.de) . Experimental nephrology, (2001) 9 (6) 436-43. Journal code: 9302239. ISSN: 1018-7782. Pub. country: Switzerland. Language: English.

AB Podocyte function appears to be regulated by vasoactive factors. In vivo podocytes express parathyroid hormone-related protein (PTHrP), the N-terminal fragment of which has vasoactive properties. Since the signaling pathway(s) of PTHrP(1-36) are unknown in podocytes, differentiated cells of a conditionally immortalized mouse podocyte cell line were studied. Gene expression of PTHrP and the PTH/PTHrP receptor was investigated by RT-PCR; protein distribution of PTHrP was examined by immunofluorescence. Accumulation of cAMP was determined by an enzyme immunoassay; [Ca2+]i was measured by fura-2 ratio imaging. PTHrP and PTH/PTHrP receptor mRNA was detected in differentiated podocytes. Immunoreactive PTHrP exhibited a granular distribution in the cytoplasm of differentiated podocytes. With regard to the signaling pathway(s) of PTHrP(1-36), a concentration-dependent increase of cAMP levels with an EC50 value of 4 +/- 2 nM was found. PTHrP(1-36) (1 microM) increased cAMP levels 5.5 +/- 1.1-fold above baseline as compared with a 25.4 +/- 4.2-fold increase in response to forskolin (10 microM). The PTH/**PTHrP receptor antagonist** PTHrP(7-34) significantly diminished the PTHrP(1-36)-induced cAMP increase. While superfusion of podocytes with bradykinin (100 nM) increased [Ca2+]i, PTHrP(1-36) (100 nM) was without effect on [Ca2+]i. However, PTHrP(1-36) attenuated the bradykinin-induced increase in [Ca2+]i. Our results suggest that PTHrP is an autocrine hormone in podocytes, which selectively activates the cAMP pathway through the PTH/PTHrP receptor.

L20 ANSWER 11 OF 32 MEDLINE on STN DUPLICATE 6

2001431698. PubMed ID: 11479139. Nitric oxide as a second messenger in parathyroid hormone-related protein signaling. Kalinowski L; Dobrucki L W; Malinski T. (Department of Chemistry and Biochemistry, Ohio University, Athens, Ohio 45701-2979, USA.) Journal of endocrinology, (2001 Aug) 170 (2) 433-40. Journal code: 0375363. ISSN: 0022-0795. Pub. country: England: United Kingdom. Language: English.

AB Parathyroid hormone (PTH)-related protein (PTHrP) is produced in smooth muscles and endothelial cells and is believed to participate in the local regulation of vascular tone. No direct evidence for the activation of endothelium-derived nitric oxide (NO) signaling pathway by PTHrP has been found despite attempts to identify it. Based on direct in situ measurements, it is reported here for the first time that the human PTH/PTHrP receptor analogs, hPTH(1--34) and hPTHrP(1--34), stimulate NO release from a single endothelial cell. A highly sensitive porphyrinic microsensor with a response time of 0.1 ms and a detection limit of 1 nmol/l was used for the measurement of NO. Both hPTH(1--34) and hPTHrP(1--34) stimulated NO release at nanomolar concentrations. The peak concentration of 0.1 micromol/l hPTH(1--34)- and 0.1 micromol/l hPTHrP(1--34)-stimulated NO release was 175+/-9 and 248+/-13 nmol/l respectively. This represents about 30%--40% of maximum NO concentration recorded in the presence of (0.1 micromol/l) calcium ionophore. Two competitive PTH/**PTHrP receptor antagonists**, 10 micromol/l [Leu(11),d -Trp(12)]-hPTHrP(7--34)amide and 10 micromol/l [Nle(8,18),Tyr(34)]-bPTH(3--34)amide, were equipotent in antagonizing hPTH(1--34)-stimulated NO release; [Leu(11),d -Trp(12)]-hPTHrP(7--34)amide was more potent than [Nle(8,18),Tyr(34)]-bPTH(3--34)amide in inhibiting

of NO release is through PTH/PTHrP receptors and is mediated via the calcium/calmodulin pathway.

L20 ANSWER 12 OF 32 MEDLINE on STN DUPLICATE 7
2001305651. PubMed ID: 11092394. Parathyroid hormone-related peptide stimulates proliferation of highly tumorigenic human SV40-immortalized breast epithelial cells. Cataisson C; Lieberherr M; Cros M; Gauville C; Graulet A M; Cotton J; Calvo F; de Vernejoul M C; Foley J; Bouizar Z. (Institut National de la Sante et de la Recherche Medicale U349, Centre Viggo Petersen, Hopital Lariboisiere, Paris, France.) Journal of bone and mineral research : official journal of the American Society for Bone and Mineral Research, (2000 Nov) 15 (11) 2129-39. Journal code: 8610640. ISSN: 0884-0431. Pub. country: United States. Language: English.

AB Parathyroid hormone-related protein (PTHrP) is the main mediator of humoral hypercalcemia of malignancy (HHM) and it is produced by many tumors, including breast cancers. Breast epithelial cells as well as breast cancer tumors and cell lines have been reported as expressing PTHrP and the PTH/PTHrP receptor, suggesting that PTHrP may act as an autocrine factor influencing proliferation or differentiation of these cell types. We investigated PTHrP gene expression, PTH/PTHrP receptor signaling, and PTHrP-induced mitogenesis in three immortalized human mammary epithelial cell lines that exhibit differential tumorigenicity. The most tumorigenic cells expressed the highest levels of PTHrP messenger RNA (mRNA) and protein. We used reverse-transcription polymerase chain reaction (RT-PCR) and immunoblotting to detect the PTH/PTHrP receptor transcripts and proteins in all of the three cell lines. Treatment with human PTHrP(1-34) [hPTHrP(1-34)] and hPTH(1-34) increased intracellular cyclic adenosine monophosphate (cAMP) but not free Ca2+ in the nontumorigenic line. These agonists increased both cAMP and free Ca2+ levels in the moderately tumorigenic line, but only increased free Ca2+ in the highly tumorigenic line. Application of the PTH/**PTHrP receptor antagonist** [Asn10,Leu11,D Trp12]PTHrP(7-34) or PTHrP antibodies reduced [3H]thymidine incorporation in a dose-dependent fashion in the highly tumorigenic cell line but did not affect the other lines. Thus, treatment with a PTH/**PTHrP receptor antagonist** reduced cell proliferation, suggesting that PTHrP signaling mediated by the phospholipase C (PLC) pathway stimulates proliferation of a highly tumorigenic immortalized breast epithelial cell line.

L20 ANSWER 13 OF 32 MEDLINE on STN DUPLICATE 8
2000496492. PubMed ID: 10974662. Parathyroid hormone(1-34) and parathyroid hormone-related protein(1-34) stimulate calcium release from human syncytiotrophoblast basal membranes via a common receptor. Farrugia W; de Gooyer T; Rice G E; Moseley J M; Wlodek M E. (Department of Physiology, University of Melbourne, Victoria 3010, Australia.) Journal of endocrinology, (2000 Sep) 166 (3) 689-95. Journal code: 0375363. ISSN: 0022-0795. Pub. country: ENGLAND: United Kingdom. Language: English.

AB The placental syncytiotrophoblast is the site for mineral and nutrient exchange across the maternal-fetal interface. It has been proposed that parathyroid hormone-related protein (PTHrP) is a key factor in the maintenance of a maternal-fetal calcium gradient. Using simultaneously prepared microvillous (maternal facing) and basal (fetal facing) syncytiotrophoblast membranes from term human placentae (n=8), we determined the relative contribution of PTH(1-34), PTHrP(1-34) and PTHrP(67-94) to the regulation of syncytiotrophoblast calcium efflux. The vesicles had correct right-side-out membrane orientation and specific markers validated the fractionation of microvillous and basal membrane

presence of the PTH/[illegible] receptor (PTHrP(7-34)). Midmolecule PTHrP(67-94) had no significant effect on basal membrane calcium efflux. PTH(1-34), PTHrP(1-34) or PTHrP(67-94) had no significant effects on MVM calcium efflux. This study, using the human syncytiotrophoblast in vitro membrane system, demonstrated that PTHrP(1-34) and PTH(1-34) stimulate calcium transport across the basal, but not microvillous, syncytiotrophoblast membrane vesicles, mediated via the PTH/PTHrP receptor.

L20 ANSWER 14 OF 32 MEDLINE on STN DUPLICATE 9
2001028365. PubMed ID: 10996344. Expression of parathyroid hormone-related protein in human and experimental atherosclerotic lesions: functional role in arterial intimal thickening. Ishikawa M; Akishita M; Kozaki K; Toba K; Namiki A; Yamaguchi T; Orimo H; Ouchi Y. (Department of Geriatric Medicine, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, 113-8655, Tokyo, Japan.) Atherosclerosis, (2000 Sep) 152 (1) 97-105. Journal code: 0242543. ISSN: 0021-9150. Pub. country: Ireland. Language: English.

AB We investigated the expression of parathyroid hormone-related protein (PTHrP) in atherosclerotic lesions and the role of PTHrP in the development of arterial neointima formation. Immunohistochemical staining of PTHrP in the neointima of rat aorta produced by balloon injury and of rat femoral artery produced by non-obstructive polyethylene cuff placement, and in the atherosclerotic lesion of human coronary artery was performed using anti-human PTHrP-(1-34) antibody. Anti-muscle actin antibody, HHF-35, and anti-macrophage antibody, HAM-56, were used to identify smooth muscle cells and macrophages, respectively. Immunoreactivity of PTHrP was detected in the thickened intima of rat and human lesions where the predominant cell types were smooth muscle cells or macrophages dependently on the lesion type. In the next series of experiments, we examined the effect of PTHrP on the development of cuff-induced intimal thickening of rat femoral artery. Either PTHrP-(1-34) or PTHrP-(7-34), a PTH/**PTHrP receptor antagonist**, suspended in pluronic F-127 gel was locally applied around the rat femoral artery. Intimal thickening induced by cuff placement was evaluated 2 weeks later. PTHrP-(1-34) dose-dependently inhibited intimal thickening determined as intima/media ratio and % stenosis whereas PTHrP-(7-34) dose-dependently enhanced that. These results suggest that PTHrP, which is expressed in atherosclerotic lesions, inhibits the development of neointimal formation.

L20 ANSWER 15 OF 32 CAPLUS COPYRIGHT 2004 ACS on STN
1998:764302 Document No. 130:10622 Antibody to parathyroid hormone-related peptide (PTHrP) or the **PTHrP receptor antagonist** as a cancerous cachexia remedy. Sato, Koh; Tunenari, Toshiaki; Ishii, Kimie (Chugai Seiyaku Kabushiki Kaisha, Japan). PCT Int. Appl. WO 9851329 A1 19981119, 125 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (Japanese). CODEN: PIXXD2. APPLICATION: WO 1998-JP2116 19980513. PRIORITY: JP 1997-125505 19970515; JP 1997-194445 19970718.

AB Disclosed is a cancerous cachexia remedy comprising a substance inhibiting the binding of a parathyroid hormone-related peptide (PTHrP) and its [illegible] of an antagonist against the

L20 ANSWER 16 OF 32 MEDLINE on STN
1998405699. PubMed ID: 9736292. Renovascular parathyroid hormone-related protein in spontaneously hypertensive rats: dilator or trophic factor?. Fiaschi-Taesch N; Endlich N; Massfelder T; Endlich K; Stewart A F; Helwig J J. (Pharmacology Department, University Louis Pasteur School of Medicine, Strasbourg, France.) Kidney international. Supplement, (1998 Sep) 67 S207-10. Journal code: 7508622. ISSN: 0098-6577. Pub. country: United States. Language: English.

AB Parathyroid hormone-related protein (PTHrP) is expressed throughout the renovascular system, and it dilates renal vessels, increases renal blood flow and glomerular filtration rate, and stimulates renin release. Mechanical forces and experimental hypertension have been shown to stimulate PTHrP expression in smooth muscles, suggesting a negative feedback control of vascular tone by PTHrP in hypertension. In this study, we compared the impact of a **PTHrP receptor antagonist**, PTHrP (7-34), and a PTHrP receptor agonist, PTHrP (1-36), on the vascular resistance of perfused kidneys isolated from spontaneously hypertensive rats (SHR) and Wistar Kyoto rats (WKY). Endogenous PTHrP appears not to act as a renal vasodilator in either WKY or SHR. However, the vasodilation following infused PTHrP (1-36) is blunted markedly in SHR, possibly due to desensitization or down-regulation of PTH/PTHrP receptors. Negative feedback control of vascular tone by PTHrP in SHR thus appears unlikely. The results raise the question of whether endogenous renovascular PTHrP behaves rather as a growth factor than as a vasodilator.

L20 ANSWER 17 OF 32 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
1998298049 EMBASE Renovascular parathyroid hormone-related protein in spontaneously hypertensive rats: Dilator or trophic factor?. Fiaschi-Taesch N.; Endlich N.; Massfelder T.; Endlich K.; Stewart A.F.; Helwig J.-J.. Dr. J.-J. Helwig, CJF INSERM 9409, EA MENRT 2307, 11 rue Humann, F-67085 Strasbourg, France. jean-jacques.helwig@pharmaco-ulp.u-strasbg.fr. Kidney International, Supplement 54/67 (S207-S210) 1998. Refs: 26.
ISSN: 0098-6577. CODEN: KISUDF. Pub. Country: United States. Language: English. Summary Language: English.

AB Parathyroid hormone-related protein (PTHrP) is expressed throughout the renovascular system, and it dilates renal vessels, increases renal blood flow and glomerular filtration rate, and stimulates renin release. Mechanical forces and experimental hypertension have been shown to stimulate PTHrP expression in smooth muscles, suggesting a negative feedback control of vascular tone by PTHrP in hypertension. In this study, we compared the impact of a **PTHrP receptor antagonist**, PTHrP (7-34), and a PTHrP receptor agonist, PTHrP (1-36), on the vascular resistance of perfused kidneys isolated from spontaneously hypertensive rats (SHR) and Wistar Kyoto rats (WKY). Endogenous PTHrP appears not to act as a renal vasodilator in either WKY or SHR. However, the vasodilation following infused PTHrP (1-36) is blunted markedly in SHR, possibly due to desensitization or down-regulation of PTH/PTHrP receptors. Negative feedback control of vascular tone by PTHrP in SHR thus appears unlikely. The results raise the question of whether endogenous renovascular PTHrP behaves rather as a growth factor than as a vasodilator.

L20 ANSWER 18 OF 32 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
1998:677175 The Genuine Article (R) Number: 115KA. Renovascular parathyroid

BLACKWELL SCIENCE LTD.
Pub. country: FRANCE. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Parathyroid hormone-related protein (PTHrP) is expressed throughout the renovascular system, and it dilates renal vessels, increases renal blood flow and glomerular filtration rate, and stimulates renin release. Mechanical forces and experimental hypertension have been shown to stimulate PTHrP expression in smooth muscles, suggesting a negative feedback control of vascular tone by PTHrP in hypertension. In this study, we compared the impact of a **PTHrP receptor antagonist**, PTHrP (7-34), and a PTHrP receptor agonist, PTHrP (1-36). on the vascular resistance of perfused kidneys isolated from spontaneously hypertensive rats (SHR) and Wistar Kyoto rats (WKY). Endogenous PTHrP appears not to act as a renal vasodilator in either WKY or SHR. However, the vasodilation following infused PTHrP (1-36) is blunted markedly in SHR, possibly due to desensitization or down-regulation of PTH/PTHrP receptors. Negative feedback control of vascular tone by PTHrP in SHR thus appears unlikely. The results raise the question of whether endogenous renovascular PTHrP behaves rather as a growth factor than as a vasodilator.

L20 ANSWER 19 OF 32 MEDLINE on STN DUPLICATE 11

1998204291. PubMed ID: 9544732. Amino-terminal fragment (1-34) of parathyroid hormone-related protein inhibits migration and proliferation of cultured vascular smooth muscle cells. Ishikawa M; Akishita M; Kozaki K; Toba K; Namiki A; Yamaguchi T; Orimo H; Ouchi Y. (Department of Geriatrics, Faculty of Medicine, University of Tokyo, Japan.) Atherosclerosis, (1998 Jan) 136 (1) 59-66. Journal code: 0242543. ISSN: 0021-9150. Pub. country: Ireland. Language: English.

AB We investigated the effects of amino-terminal fragment (1-34) of parathyroid hormone-related protein [PTHrP-(1-34)] on the migration and proliferation of vascular smooth muscle cells (VSMCs). Cultured VSMCs (5-9th passage) obtained from the aortas of male Wistar rats were used in this study. Migration of VSMCs was assessed using a modified Boyden's chamber. Proliferation of VSMCs was evaluated by measuring [3H]thymidine incorporation and counting cell numbers. PTHrP-(1-34) inhibited 10% fetal bovine serum (FBS)-induced increase in migration of VSMCs (61% of control at 1 micromol/l) in a concentration-dependent manner. PTHrP-(1-34) also inhibited 5% FBS-induced increase in [3H]thymidine incorporation (37% of control at 1 micromol/l) and cell number of VSMCs (33% of control at 1 micromol/l) in a concentration-dependent manner. Parathyroid hormone (PTH)-(1-34) inhibited the migration and DNA synthesis of VSMCs to a similar extent. PTHrP-(7-34), a PTH/**PTHrP receptor antagonist**, significantly inhibited these effects of PTHrP and PTH. PTHrP-(1-34) also inhibited platelet-derived growth factor-BB (5 ng/ml)-induced migration and DNA synthesis of VSMCs. These findings suggest that PTHrP-(1-34) inhibits the migration and proliferation of VSMCs through PTH/PTHrP receptors.

L20 ANSWER 20 OF 32 MEDLINE on STN DUPLICATE 12

1998199131. PubMed ID: 9538330. Effect of antagonism of the parathyroid hormone (PTH)/PTH-related protein receptor on decidualization in rat uterus. Williams E D; Major B J; Martin T J; Moseley J M; Leaver D D. (Department of Pharmacology, University of Melbourne, Parkville, Victoria, Australia.) Journal of reproduction and fertility, (1998 Jan) 112 (1) 59-67. Journal code: 0376367. ISSN: 0022-4251. Pub. country: ENGLAND: United Kingdom. Language: English.

(PTHrP) was detected at 32.8 +/- 3.9

[Asn10,Leu11]PTHrP(7-34) amide, into the uterine lumen during pregnancy in rats resulted in excessive decidualization. This effect was also observed after intrauterine infusion of a monoclonal antibody raised against PTHrP. The effect of infusion of PTH/**PTHrP receptor antagonist** was dependent upon successful implantation, was dose-dependent and confined to the treated horn. A decrease in the number of apoptotic decidual cells in antagonist-infused uterine horns compared with vehicle or non-infused horns was detected immunohistochemically at day 13 of pregnancy, and this decrease is likely to contribute to the 'over-decidualization' observed. In pseudopregnant rats, infusion of PTH/**PTHrP receptor antagonist** into the uterine lumen resulted in an increase in uterine wet weight of the infused horn compared with the non-infused horn, indicating a direct effect on deciduoma formation. Thus, activation of the PTH/PTHrP receptor by locally produced PTHrP appears to be crucial for normal decidualization during pregnancy in rats.

L20 ANSWER 21 OF 32 MEDLINE on STN DUPLICATE 13

97325812. PubMed ID: 9182824. Control of hair growth with parathyroid hormone (7-34). Schilli M B; Ray S; Paus R; Obi-Tabot E; Holick M F. (Department of Medicine, Boston University Medical Center, Massachusetts 02118, USA.) Journal of investigative dermatology, (1997 Jun) 108 (6) 928-32. Journal code: 0426720. ISSN: 0022-202X. Pub. country: United States. Language: English.

AB Parathyroid hormone (PTH) related peptide (PTHrP) is thought to influence the proliferation and differentiation of the epidermis and hair follicle. As a means of elucidating the biologic function of PTHrP on the hair follicle, a PTHrP analog PTH (7-34), which is a PTH/**PTHrP receptor antagonist**, was given intraperitoneally twice daily to C57 BL/6 mice at different stages of the hair cycle. PTH (7-34) induced 99 +/- 4.5% (mean +/- SEM) of resting telogen hair follicles into a proliferative (anagen) state, whereas 100% of the hair follicles in the control group remained in telogen. To determine whether this peptide influenced the progression of the hair follicles from anagen to catagen (hair follicle maturation and regression), groups of mice that were either spontaneously in or induced to anagen received either PTH (7-34) or placebo. Morphometric analysis of the hair follicles from the middle back region of the spontaneous anagen mice that received PTH (7-34) revealed that 19 +/- 4% (mean +/- SEM) of the follicles were in anagen VI, whereas none (0%) were in anagen in the control group. Similarly, in induced anagen mice treated with PTH (7-34), 22.3 +/- 1.4 (mean +/- SEM) of the follicles were in anagen VI compared to only 1.3 +/- 0.7% in the control mice. Together these observations suggest that PTHrP is a hair follicle morphogen that may be a major factor responsible for controlling the hair cycle. These studies provide a new insight for development of PTHrP analogs for a wide variety of disorders related to disturbances of hair cycling.

L20 ANSWER 22 OF 32 MEDLINE on STN DUPLICATE 14

97289447. PubMed ID: 9144352. Synovial fluids from patients with osteoarthritis and rheumatoid arthritis contain high levels of parathyroid hormone-related peptide. Kohno H; Shigeno C; Kasai R; Akiyama H; Iida H; Tsuboyama T; Sato K; Konishi J; Nakamura T. (Department of Orthopaedic Surgery, Graduate School of Medicine, Kyoto University, Sakyo, Japan.) Journal of bone and mineral research : official journal of the American Society for Bone and Mineral Research, (1997 May) 12 (5) 847-54. Journal code: 8610640. ISSN: 0884-0431. Pub. country: United States. Language:

longer peptides and a radioimmunoassay (RIA) specific to the carboxy-terminal portion of hPTHrP, were 3.2 +/- 0.3 pmol of hPTHrP(1-86)/l and 61 +/- 7.0 pmol of hPTHrP(109-141)/l in OA patients (mean +/- SE, n = 23), and 4.8 +/- 0.8 pmol of hPTHrP(1-86)/l and 164 +/- 30 pmol of hPTHrP(109-141)/l in RA patients (n = 26). Synovial fluid PTHrP levels distributed above the normal plasma reference ranges in each assay (0.7-2.6 pmol of hPTHrP(1-86)/l; 16-60.6 pmol of hPTHrP(109-141)/l). After concentration using sequential cation-exchange and reverse-phase chromatography, synovial fluid exhibited the activity that stimulated cyclic adenosine monophosphate (cAMP) accumulation in osteoblastic ROS 17/2.8 cells expressing PTH/PTHrP receptors. The cAMP accumulation activity in synovial fluid was sensitive to coincubation with excess hPTHrP(3-40), a PTH/**PTHrP receptor antagonist**, and was completely neutralized by preincubation with a monoclonal antibody specific to hPTHrP but not PTH. Immunohistochemical analysis of RA synovium revealed that PTHrP was localized in fibroblast-like cells in the synovial pannus invading articular cartilage. Our data show that PTHrP is produced locally by the diseased synovial tissue and released into synovial fluid at high concentrations, allowing us to hypothesize that PTHrP plays a novel role as a paracrine/autocrine factor in the pathology of OA and RA.

L20 ANSWER 23 OF 32 MEDLINE on STN DUPLICATE 15

97435424. PubMed ID: 9290155. Vascular effects of PTHrP (1-34) and PTH (1-34) in the human fetal-placental circulation. Macgill K; Moseley J M; Martin T J; Brennecke S P; Rice G E; Wlodek M E. (Department of Perinatal Medicine, Royal Women's Institute of Medical Research, Fitzroy, Victoria, Australia.) Placenta, (1997 Sep) 18 (7) 587-92. Journal code: 8006349. ISSN: 0143-4004. Pub. country: ENGLAND: United Kingdom. Language: English.

AB The aim of this study was to examine the vasodilatory effects of parathyroid hormone-related protein (PTHrP) (1-34) and parathyroid hormone (PTH) (1-34) on the human fetal-placental circulation utilising an in vitro placental perfusion model. In all experiments, the vasculature of an isolated human placental cotyledon was pre-constricted with the thromboxane A2 mimetic U46619. A simple dose of PTHrP (1-34) or PTH (1-34) (1.7-300 nM) was then infused into the fetal-placental circulation of the cotyledon. In other experiments, cotyledons were repeatedly infused with PTHrP (1-34) or PTH (1-34) (51.3 nM). Vasodilatory responses were significantly reduced in response to repeated exposure to PTHrP (1-34) ($P < 0.001$), indicating that this peptide desensitizes the fetal-placental vasculature. PTHrP (1-34) and PTH (1-34) equipotently stimulated a significant vasodilation of the fetal-placental circulation ($P < 0.0001$). The **PTHrP receptor antagonist** [Asn10, Leu 11]PTHrP (7-34) (102 nM) was infused in U46619-constricted placentae in the presence and absence of PTHrP (1-34) (10.2 nM). The PTHrP antagonist alone had no significant effect in the fetal-placental circulation. The antagonist significantly attenuated the response to PTHrP (1-34) ($P < 0.015$). Based on the data obtained in this study it is suggested that locally produced PTHrP (1-34) may be involved in the regulation of normal human fetal-placental vascular tone in autocrine and/or paracrine fashion.

L20 ANSWER 24 OF 32 MEDLINE on STN DUPLICATE 16

96366780. PubMed ID: 8770894. The human PTH2 receptor: binding and signal transduction properties of the stably expressed recombinant receptor. Behar V; Pines M; Nakamoto C; Greenberg Z; Bisello A; Stueckle S M; Bessalle R; Usdin T B; Chorev M; Rosenblatt M; Suva L J. (Division of Bone

receptor, ... PTH-(1-34) and not the corresponding N-terminal (1-34) region of the functionally and structurally related hormone, PTH-related protein (PTHrP). A total of 20 distinct clones displaying different levels of PTH-responsive cAMP production were analyzed. None responded to PTHrP-(1-34). One of these clones (BP-16), displaying maximal PTH responsiveness, was chosen for more detailed evaluation. The BP-16 clone (and the parental HEK-293 cell line lacking both the hPTH/PTHrP receptor and the hPTH2 receptor) were examined for PTH binding, PTH-stimulated cAMP accumulation, PTH-stimulated changes in intracellular calcium ([Ca2+]i) levels, and hPTH2 receptor messenger RNA expression. In addition, we studied the photomediated cross-linking of a potent PTH agonist, namely [Nle8,18,Lys13 (epsilon-pBz2), 2-L-Nal23,Tyr34]bPTH(1-34)NH2 (K13), to the hPTH2 receptor on BP-16 cells. Photoaffinity cross-linking identified an approximately 90-kDa cell membrane component that was specifically competed by PTH-(1-34) and other receptor-interacting ligands. PTH-(1-34) and K13 are potent stimulators of both cAMP accumulation and increases in (Ca2+]i levels, and both bind to the hPTH2 receptor with high affinity (apparent Kd, 2.8 +/- 0.9 x 10(-8) and 8.5 +/- 1.7 x 10(-8) M, respectively). There was no apparent binding, cAMP-stimulating activity, or [Ca 2+]i signaling observed, nor was specific competition vs. binding of a PTH-(1-34) radioligand ([125I]PTH) with PTHrP-(1-34)NH2 found. PTHrP-(1-34) failed to inhibit cross-linking of the hPTH2 receptor by radiolabeled K13 ([125I]K13). However, effective competition vs. [125I]PTH and [125I]K13 binding and [125I]K13 cross-linking were observed with the potent PTH/**PTHrP receptor antagonists**, PTHrP-(7-34)NH2 and PTH-(7-34)NH2. PTHrP-(7-34)NH2 was shown to be a partial agonist that weakly stimulates both cAMP accumulation and increases in [Ca 2+]i levels in BP-16 cells. These data suggest that the hPTH2 receptor is distinct from the hPTH/PTHrP receptor in the structural features it requires for ligand binding in the family of PTH and PTHrP peptides.

L20 ANSWER 25 OF 32 MEDLINE on STN DUPLICATE 17

96217275. PubMed ID: 8641188. Effect of endogenously produced parathyroid hormone-related peptide on growth of a human hepatoma cell line (Hep G2). Li H; Seitz P K; Selvanayagam P; Rajaraman S; Cooper C W. (Department of Pharmacology, University of Texas Medical Branch, Galveston 77555, USA.) Endocrinology, (1996 Jun) 137 (6) 2367-74. Journal code: 0375040. ISSN: 0013-7227. Pub. country: United States. Language: English.

AB A well differentiated human hepatoma cell line (Hep G2) was used to explore potential roles for PTH-related peptide (PTHrP) as an autocrine/paracrine growth factor. Using Northern analysis or reverse transcription-PCR, Hep G2 cells were found to express messenger RNAs for both PTHrP and the cloned PTH/PTHrP receptor, and the cells exhibited specific binding for [125I]PTHrP(1-36). Hep G2 growth medium was found to contain relatively large amounts of immunoreactive PTHrP (30 vs. 1-2 pM in medium not exposed to cells), and the PTHrP in growth medium (conditioned medium) was shown to contain N-terminal PTHrP biological activity, as assessed by the ability of the medium to stimulate cAMP production in rat osteosarcoma cells (ROS 17/2.8). Conditioned medium produced a dose-dependent severalfold increase in ROS cell cAMP that could be blocked by the **PTHrP receptor antagonist** [Asn10,Leu11,DTrp12]PTHrP-(7-34). PTHrP in Hep G2 cells also was detected by immunocytochemistry using antiserum to either synthetic PTHrP-(1-34) or recombinant PTHrP-(-5 to 139). Furthermore, these antisera were found to inhibit the ability of PTHrP-(1-34) to stimulate ROS cell cAMP production. ... (1:800-1:100 dilution) was added to subconfluent Hep

addition of antiserum to PTHrP resulted in increased cell growth, the findings suggest that PTHrP can function as an autocrine or paracrine growth factor to suppress the growth of these human hepatoma cells.

L20 ANSWER 26 OF 32 MEDLINE on STN DUPLICATE 18

97017917. PubMed ID: 8864534. Effect of intrarenally infused parathyroid hormone-related protein on renal blood flow and glomerular filtration rate in the anaesthetized rat. Massfelder T; Parekh N; Endlich K; Saussine C; Steinhausen M; Helwig J J. (Laboratoire de Physiologie Cellulaire Renale, Faculte de Medecine, Universite Louis Pasteur, CJF INSERM 9409, Strasbourg, France.) British journal of pharmacology, (1996 Aug) 118 (8) 1995-2000. Journal code: 7502536. ISSN: 0007-1188. Pub. country: ENGLAND: United Kingdom. Language: English.

AB 1. Parathyroid hormone-related protein (PTHrP) is expressed in the kidney and acts on vascular PTH/ PTHrP receptors to vasodilate the isolated kidney and to stimulate renin release. However, effects of PTHrP on renal blood flow (RBF) and glomerular filtration rate (GFR) in vivo have not been assessed in the absence of its cardiac, peripheral and central effects. We investigated the renal effects of PTH and PTHrP infused into the left renal artery of anaesthetized rats. 2. Intrarenal infusions, adjusted to generate increasing concentrations of human PTHrP(1-34) and rat PTH(1-34) in renal plasma (2 x 10(-11) to 6 x 10(-9) M) produced a comparable dose-dependent increase in RBF. The rise was 4% at the lowest and 34% at the highest concentrations of peptides. Up to a concentration of 2 x 10(-9) M, mean arterial pressure (MAP) and heart rate were not affected, but at 6 x 10(-9) M, intrarenally infused peptides reached the peripheral circulation, and caused a fall in MAP within a few minutes. While MAP returned to basal value after the last peptide infusion, RBF remained more than 10% above control for at least 30 min. 3. Two competitive PTH/**PTHrP receptor antagonists**, [Nle8,18, Tyr34]-bPTH(3-34)amide and [Leu11, D-Trp12]-hPTHrP(7-34)amide (2 x 10(-8) M) were devoid of agonist activity, but markedly antagonized the dose-dependent increase in RBF elicited by PTHrP. 4. GFR and urine flow were measured in left PTHrP-infused experimental kidney and right control kidney. Renal PTHrP concentration of 10(-10) M elevated left RBF by 10%, and GFR by 20% without significantly increasing filtration fraction, and increased urine flow by 57%. In the right control kidney GFR and diuresis did not change. 5. The results indicate that PTHrP has similar renal haemodynamic effects as PTH and increases RBF, GFR and diuresis in anaesthetized rats.

L20 ANSWER 27 OF 32 CAPLUS COPYRIGHT 2004 ACS on STN

1996:695985 Document No. 126:54998 Conformational studies of analogs of parathyroid hormone related protein (PTHrP) containing lactam-bridged side-chains. Chorev, M.; Bisello, A.; Behar, V.; Nakamoto, C.; Rosenblatt, M.; Maretto, S.; Mammi, S.; Peggion, E. (Harvard Medical School, Beth Israel Hospital, Boston, MA, 02215, USA). Peptides: Chemistry, Structure and Biology, Proceedings of the American Peptide Symposium, 14th, Columbus, Ohio, June 18-23, 1995, Meeting Date 1995, 525-526. Editor(s): Kaumaya, Pravin T. P.; Hodges, Robert S. Mayflower Scientific: Kingswinford, UK. (English) 1996. CODEN: 63NTAF.

AB The authors recently studied the conformational properties of two highly potent PTH/**PTHrP receptor antagonists**, i.e., [Leu11,D-Trp12]PTHrP(7-34)NH2 and [Ahx8,18,D-Trp12,Tyr34]PTH(7-34)NH2. In 1:1 TFE-water, both analogs adopt a helical structure comprising the sequence 15-32. In an attempt to identify the relevant elements of bioactive conformation, the authors synthesized 2 structurally constrained

upon addition of TFE.

L20 ANSWER 28 OF 32 MEDLINE on STN DUPLICATE 19
95203327. PubMed ID: 7895771. Parathyroid hormone-related protein reduces cytosolic free Ca2+ level and tension in rat aortic smooth muscle. Ishikawa M; Ouchi Y; Han S Z; Akishita M; Kozaki K; Toba K; Namiki A; Yamaguchi T; Orimo H. (Department of Geriatrics, Faculty of Medicine, University of Tokyo, Japan.) European journal of pharmacology, (1994 Nov 15) 269 (3) 311-7. Journal code: 1254354. ISSN: 0014-2999. Pub. country: Netherlands. Language: English.

AB The effect of parathyroid hormone-related protein (PTHrP) on cytosolic free Ca2+ level ([Ca2+]i) and tension in rat aortic smooth muscle was investigated with special reference to the role of production and action of cyclic AMP. Rat aortic spiral strip preparations without endothelium were treated with the acetoxymethyl ester of fura 2, and the ratio of fluorescences (R340/380), an index of [Ca2+]i, emitted from smooth muscle, was measured. The tension of the preparations was simultaneously measured. PTHrP-(1-34) produced concentration-dependent decreases both in the tension and in R340/380 increased by phenylephrine (10(-7) M). These effects were significantly inhibited by pretreatment with either PTHrP-(7-34) (10(-6) M), a **PTHrP receptor antagonist**, or with Rp diastereomer of adenosine cyclic 3',5'-phosphorothioate (RpcAMPS; 10(-4) M), a cyclic AMP-dependent protein kinase inhibitor. Dibutyryl cyclic AMP (10(-5)-10(-3.5 M) elicited effects similar to those of PTHrP-(1-34). PTHrP-(1-34) was found to significantly elevate aortic cAMP level, measured by specific radioimmunoassay, after 5 min incubation with PTHrP-(1-34). These results suggest that the decrease in [Ca2+]i is involved in the vasodilator action of PTHrP, and that the decreases both in tension and in [Ca2+]i might be attributed to cyclic AMP production stimulated by PTHrP.

L20 ANSWER 29 OF 32 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
1995:33204 Document No.: PREV199598047504. Parathyroid hormone-related protein reduces cytosolic free Ca-2+ level and tension in rat aortic smooth muscle. Ishikawa, Michiro; Ouchi, Yasuyoshi; Han, Shu-Zhong; Akishita, Masahiro; Kozaki, Koichi; Toba, Kenji; Namiki, Atsushi; Yamaguchi, Tetsu; Orimo, Hajime. Dep. Geriatrics, Fac. Med., Univ. Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113, Japan. European Journal of Pharmacology Molecular Pharmacology Section, (1994) Vol. 17, No. 3, pp. 311-317.
CODEN: EJPPET. ISSN: 0922-4106. Language: English.

AB The effect of parathyroid hormone-related protein (PTHrP) on cytosolic free Ca-2+ level ((Ca-2+)-i) and tension in rat aortic smooth muscle was investigated with special reference to the role of production and action of cyclic AMP. Rat aortic spiral strip preparations without endothelium were treated with the acetoxymethyl ester of fura 2, and the ratio of fluorescences (R340/380), an index of (Ca-2+)-i, emitted from smooth muscle, was measured. The tension of the preparations was simultaneously measured. PTHrP-(1-34) produced concentration-dependent decreases both in the tension and in R340/380 increased by phenylephrine (10-7 M). These effects were significantly inhibited by pretreatment with either PTHrP-(7-34) (10-6 M), a **PTHrP receptor antagonist**, or with Rp diastereomer of adenosine cyclic 3',5'-phosphorothioate (RpcAMPS; 10-4 M), a cyclic AMP-dependent protein kinase inhibitor. Dibutyryl cyclic AMP (10-5-to 10-3.5 M) elicited effects similar to those of PTHrP-(1-34). PTHrP-(1-34) was found to significantly elevate aortic cAMP level, measured by specific

94:755551 The Genuine Article (R) Number: [illegible]
PROTEIN REDUCES CYTOSOLIC-FREE CA2+ LEVEL AND TENSION IN RAT AORTIC SMOOTH-MUSCLE. ISHIKAWA M; OUCHI Y (Reprint); HAN S Z; AKISHITA M; KOZAKI K; TOBA K; NAMIKI A; YAMAGUCHI T; ORIMO H. UNIV TOKYO, FAC MED, DEPT GERIATR, BUNKYO KU, 7-3-1 HONGO, TOKYO 113, JAPAN (Reprint); UNIV TOKYO, FAC MED, DEPT GERIATR, BUNKYO KU, TOKYO 113, JAPAN; TOHO UNIV, OHASHI HOSP, SCH MED, DEPT INTERNAL MED 3, MEGURO KU, TOKYO 153, JAPAN. EUROPEAN JOURNAL OF PHARMACOLOGY-MOLECULAR PHARMACOLOGY SECTION (15 NOV 1994) Vol. 269, No. 3, pp. 311-317. ISSN: 0922-4106. Pub. country: JAPAN. Language: ENGLISH.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The effect of parathyroid hormone-related protein (PTHrP) on cytosolic free Ca2+ level ([Ca2+](i)) and tension in rat aortic smooth muscle was investigated with special reference to the role of production and action of cyclic AMP. Rat aortic spiral strip preparations without endothelium were treated with the acetoxymethyl ester of fura 2, and the ratio fluorescences (R340/380), an index of [Ca2+](i), emitted from smooth muscle, was measured. The tension of the preparations was simultaneously measured. PTHrP-(1-34) produced concentration-dependent decreases both in the tension in R340/380 increased by phenylephrine (10(-7) M). These effects were significantly inhibited by pretreatment with either PHTrP-(7-34) (10(-6) M), a **PTHrP receptor antagonist**, or with Rp diastereomer of adenosine cyclic 3',5'-phosphorothioate (RpcAMPS; 10-4 M), a cyclic AMP-dependent protein kinase inhibitor. Dibutyryl cyclic AMP (10(-5)-10(-35) M) elicited effects similar to those of PTHrP-(1-34), PTHrP-(1-34) was found to significantly elevate aortic cAMP level, measured by specific radioimmunoassay, after 5 min incubation with PTHrP-(1-34). These results suggest that the decrease in [Ca2+](i) is involved in the vasodilator action of PTHrP, and that the decreases both in tension and in [ca(2+)](i) might be attributed to cyclic AMP production stimulated PTHrP.

L20 ANSWER 31 OF 32 MEDLINE on STN DUPLICATE 20

93010633. PubMed ID: 1327716. A pharmacological comparison of parathyroid hormone receptors in human bone and kidney. Orloff J J; Ribaudo A E; McKee R L; Rosenblatt M; Stewart A F. (Division of Endocrinology and Metabolism, West Haven Veterans Affairs Medical Center, Connecticut 06516.) Endocrinology, (1992 Oct) 131 (4) 1603-11. Journal code: 0375040. ISSN: 0013-7227. Pub. country: United States. Language: English.

AB While abundant information is available characterizing PTH receptor properties in other species, data on human PTH receptors is very limited. We have been interested in the possibility that tissue-specific differences among human PTH receptors (i.e. bone vs. kidney) might exist. We have, therefore, compared pharmacological profiles for a wide array of PTH and PTH-related peptide (PTHrP) analogs in human osteoblast-like cells (SaOS-2) and human renal cortical membranes (RCM) using radioiodinated (Tyr36)hPTHrP(1-36)NH2 as a probe for PTH receptor function. The rank order of receptor affinity for 10 PTH/PTHrP receptor agonists tested was very similar in the bone and kidney assay systems. Binding affinity for these peptides was greater in human (h)RCMs and SaOS-2 membranes than in SaOS-2 intact cells. The relative binding affinities for (Tyr36)hPTHrP(1-36)amide, hPTH(1-34), bovine (b)PTH(1-34), and rat PTH(1-34) were similar in human RCMs, SaOS-2 membranes, and SaOS-2 cells. bPTH(1-84) and hPTHrP(1-74) both manifested lower receptor affinity than the amino-terminal analogs. Seven PTH/**PTHrP receptor antagonists** were also studied in this homologous human assay system. The binding affinity for hPTHrP(7-34)NH2 was 2- to 3-fold greater

receptors in human renal and skeletal tissues demonstrated an indistinguishable dominant 85-kilodalton receptor protein. We conclude that the binding and bioactivity profiles of a broad array of PTH and PTHrP peptides are very similar or identical in human renal and skeletal tissues. Differences relating to intact vs. broken cell preparations accounted for some variation in potency. These studies emphasize the importance of employing homologous assay systems to study PTH receptor function and the existence of interspecies differences among PTH receptors. The results support the possibility that PTH receptors in human bone and human kidney are very similar if not identical.

L20 ANSWER 32 OF 32 MEDLINE on STN DUPLICATE 21
93231354. PubMed ID: 1299622. Parathyroid hormone-related peptide can regulate the growth of human lung cancer cells, and may form part of an autocrine TGF-alpha loop. Burton P B; Knight D E. (Division of Biomedical Sciences, Kings College, London, UK.) FEBS letters, (1992 Jul 6) 305 (3) 228-32. Journal code: 0155157. ISSN: 0014-5793. Pub. country: Netherlands. Language: English.

AB Parathyroid hormone-related peptide (PTHrP) and transforming growth factor-alpha (TGF-alpha) were found to stimulate proliferation of human lung cancer cells (BEN-57). TGF-alpha stimulated PTHrP secretion from these cells. The polyclonal antisera raised against PTHrP significantly inhibited the growth of BEN-57 cells, and also the proliferation induced by TGF-alpha. Treatment of cells for up to 10 days with either a **PTHrP receptor antagonist** (PTHrP(7-34)) or PTHrP antiserum significantly inhibited the subsequent growth of these cells. We suggest that PTHrP may be a component of a complex autocrine loop involving TGF-alpha.

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L21          3 "#23-57-137-1"

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L22 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2004 ACS on STN
2002:888597 Document No. 138:3671 Angiogenesis inhibitors that block binding of PTH-related peptide to its receptor for use as antitumor agents. Saito, Hidemi; Tsunenari, Toshiaki; Onuma, Etsuro; Kato, Atsuhiko; Suzuki, Masami (Chugai Seiyaku Kabushiki Kaisha, Japan). PCT Int. Appl. WO 2002092133 A1 20021121, 110 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (Japanese). CODEN: PIXXD2. APPLICATION: WO 2002-JP4586 20020510. PRIORITY: JP 2001-140659 20010510.

AB It is found out that angiogenesis can be inhibited by a substance which inhibits the binding of a parathyroid hormone-associated peptide (e.g. PTHrP)

L22 ANSWER 2 OF 3
2000:15036 Document No. 132:73627 Therapeutics containing inhibitors for parathyroid hormone-related peptide receptor for hypercalcemic crisis. Sato, Koh; Tsunenari, Toshiaki (Chugai Seiyaku Kabushiki Kaisha, Japan). PCT Int. Appl. WO 2000000219 A1 20000106, 120 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (Japanese). CODEN: PIXXD2. APPLICATION: WO 1999-JP3433 19990625. PRIORITY: JP 1998-180143 19980626.

AB Disclosed is a therapeutic composition containing an inhibitor for parathyroid hormone-related peptide receptor (PTHrP) for treating hypercalcemic crisis, that is frequently associated with malignant tumors, by using an antagonist such as an antibody to PTHrP. A nude mice or nude rat implanted with human pancreatic tumor-derived FA-6 cells or human lung cancer-derived LC-6-JCK cells was used as a disease model to evaluate the effects of the therapeutics to hypercalcemia of malignancy. Mouse monoclonal antibody number **23-57-137-1** and its humanized derivative hMBC(q) were used to demonstrate their rapid and long-lasting effects on reducing blood Ca level, which are more desirable as compared to calcitonin, in a rat model.

L22 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2004 ACS on STN
1998:764302 Document No. 130:10622 Antibody to parathyroid hormone-related peptide (PTHrP) or the PTHrP receptor antagonist as a cancerous cachexia remedy. Sato, Koh; Tunenari, Toshiaki; Ishii, Kimie (Chugai Seiyaku Kabushiki Kaisha, Japan). PCT Int. Appl. WO 9851329 A1 19981119, 125 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (Japanese). CODEN: PIXXD2. APPLICATION: WO 1998-JP2116 19980513. PRIORITY: JP 1997-125505 19970515; JP 1997-194445 19970718.

AB Disclosed is a cancerous cachexia remedy comprising a substance inhibiting the binding of a parathyroid hormone-related peptide (PTHrP) and its receptor, which inhibitor may consist of an antagonist against the receptor or an antibody to the PTHrP. Anti-cachexia effects of humanized mouse monoclonal antibody **23-57-137-1** were observed by using the nude mice transplanted with OCC-1 human buccal cancer cell, which effects were based on the blood level of Ca, body weight, and survival.

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'IS' IS NOT A VALID FORMAT FOR FILE 'CAPLUS'

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HITRN ------- HIT RN and its text modification
HITSTR ------ HIT RN, its text modification, its CA index name, and
its structure diagram
HITSEQ ------ HIT RN, its text modification, its CA index name, its
structure diagram, plus NTE and SEQ fields
FHITSTR ----- First HIT RN, its text modification, its CA index name, and
its structure diagram
FHITSEQ ----- First HIT RN, its text modification, its CA index name, its
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APPS -------- AI, PRAI

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IND --------- Indexing data
IPC --------- International Patent Classifications
MAX --------- ALL, plus Patent FAM, RE
PATS -------- PI, SO
SAM --------- CC, SX, TI, ST, IT
SCAN -------- CC, SX, TI, ST, IT (random display, no answer numbers;
SCAN must be entered on the same line as the DISPLAY,
e.g., D SCAN or DISPLAY SCAN)
STD --------- BIB, IPC, and NCL

IABS -------- ABS, indented with text labels
IALL -------- ALL, indented with text labels
IBIB -------- BIB, indented with text labels
IMAX -------- MAX, indented with text labels
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OIBIB ------- OBIB, indented with text labels

SBIB -------- BIB, no citations
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containing hit terms
HITRN ------- HIT RN and its text modification
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its structure diagram
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structure diagram, plus NTE and SEQ fields
FHITSTR ----- First HIT RN, its text modification, its CA index name, and
its structure diagram
FHITSEQ ----- First HIT RN, its text modification, its CA index name, its
structure diagram, plus NTE and SEQ fields
KWIC -------- Hit term plus 20 words on either side
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To display a particular field or fields, enter the display field codes. For a list of the display field codes, enter HELP DFIELDS at an arrow prompt (=>). Examples of formats include: TI; TI,AU; BIB,ST; TI,IND; TI,SO. You may specify the format fields in any order and the information will be displayed in the same order as the format specification.

All of the formats (except for SAM, SCAN, HIT, HITIND, HITRN, HITSTR, FHITSTR, HITSEQ, FHITSEQ, KWIC, and OCC) may be used with DISPLAY ACC to view a specified Accession Number.
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L22 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2002:888597 CAPLUS
DN 138:3671
TI Angiogenesis inhibitors that block binding of PTH-related peptide to its receptor for use as antitumor agents
IN Saito, Hidemi; Tsunenari, Toshiaki; Onuma, Etsuro; Kato, Atsuhiko; Suzuki, Masami

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      PATENT NO.        KIND   DATE            APPLICATION NO.   DATE
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PI    WO 2002092133     A1     20021121        WO 2002-JP4586    20020510
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              TJ, TM
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     06 APR 2004
L1         30695 S "AVP"
L2            29 S L1 AND "PTHRP"
L3             7 DUP REMOVE L2 (22 DUPLICATES REMOVED)
L4           200 S ANTI-PTHRP
L5             0 S L4 AND "AVP"
L6             0 S L4 AND VASOPRESSIN
L7             3 S L4 AND VOMITING
L8             1 DUP REMOVE L7 (2 DUPLICATES REMOVED)
L9             3 S L4 AND POLYURIA
L10            1 DUP REMOVE L9 (2 DUPLICATES REMOVED)
L11            3 S L4 AND ANTIHYPERCALCEMIC ACTIVITY
L12            1 DUP REMOVE L11 (2 DUPLICATES REMOVED)
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L15           15 S L13 AND "PTHRP 1-34"
L16          112 S PTHRP RECEPTOR ANTAGONIST
L17           22 S L16 AND BINDING
L18            6 S L17 AND ANTIBODY
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=> s vasopressin level
L23         2943 VASOPRESSIN LEVEL

=> s l23 and symptom
L24           95 L23 AND SYMPTOM

=> s l24 and treatment
L25           12 L24 AND TREATMENT

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2003074503 EMBASE Electrolyte derangements and diuretic misuse in the elderly. Bartoli E.; Castello L.; Fumo E.; Pirisi M.. E. Bartoli, Cattedra di Medicina Interna, Dipartimento di Scienze Mediche, Univ. Studi Piemonte Orientale A., Via Solaroli, 17, I-28100 Novara, Italy. ettore.bartoli@med.unipmn.it. Archives of Gerontology and Geriatrics 35/SUPPL. 8 (43-52) 2002.
Refs: 15.
ISSN: 0167-4943. CODEN: AGGEDL. Pub. Country: Ireland. Language: English. Summary Language: English.

AB Hypo- and hypernatremia occur frequently in elderly patients, representing severe complications leading to adverse events and, ultimately, to death. Hyponatremia develops either as a consequence of excessive water retention or solute depletion, or a combination of both. The normal kidney is capable of excreting any water excess, preventing the occurence of hypo-osmolar syndromes. Therefore, hyponatremia due to water retention requires an important defect in renal diluting ability. This commonly occurs because of central hypovolemia, nephron hypoperfusion, excessive fractional reabsorption in the proximal tubule and reduced fluid delivery to the distal nephron. Under these circumstances, while solute flee water formation is curbed by the reduced delivery of fluid, ADH-independent water abstraction can be unaltered, thus reclaiming a larger fraction of the inflow to the distal nephron. This leads to the excretion of a reduced volume of concentrated urine even in the absence of ADH, causing water retention and reduced diluting power. ADH secretion and high **vasopressin levels** in the plasma, caused by altered hypothalamic function, further contribute to the onset of hyponatremia. Drugs, heart failure, renal failure, cerebrovascular disease are frequent conditions capable of initiating this pathophysiological sequence. The most frequent cause of low plasma sodium in old age is represented by diuretic-induced Nadepletion. To the extent that sodium loss during diuretic **treatment** reduces the effective plasma volume and activates thirst, volume is defended by water intake, leading to dilution of residual solutes by a normal volume of solvent. In the aging subject, diuretic-induced K-depletion may represent a more common cause of hyponatremia than Na-loss. Hypernatremia is probably more common than hyponatremia in the elderly. It is caused almost exclusively by important water loss without equivalent solute losses. Dehydration can be caused by fever, coma, insufficient water supply during hospitalization or nursing home care, loss of thirst mechanism, diarrhea, vomiting, heat stroke, mental clouding, stroke, dementia and cerebrovascular disease. Careful clinical examination of the patients, and medical history identify the **symptoms** of the effective volume contraction due to solute depletion, as opposed to the prevalent signs of cerebral edema and hypertension characterizing water retention. The **treatment** of excess solvent retention requires techniques of excreting large volumes of hypotonic fluids with the aid of loop diuretics, while reinfusing part of the volume lost with hypertonic solutions that quantitatively replace the solutes excreted. The **treatment** of solute depletion requires the replenishment of either sodium, or potassium, or both, delivered with the minimal volume required. Water deficit and the attendant hypernatremia can be corrected by replenishing with either hypotonic solutions or with dextrose-containing f{uids the calculated losses. Simple mathematical formulas allow the correct calculations of the volumes and amounts of electrolytes necessary for replenishing the losses, effectively correcting hypo or hypernatremia.

AB Left ventricular systolic dysfunction is associated with neurohormonal activation which contributes to progressive ventricular remodeling and worsening clinical heart failure. Renin-angiotensin-aldosterone and sympathetic nervous systems are activated, not only in patients with clinically overt heart failure, but also in patients with asymptomatic or minimally symptomatic left ventricular systolic dysfunction. Activation of the angiotensin and adrenergic systems produces deleterious effects on systemic and coronary hemodynamics, promotes myocyte hypertrophy and fibroblast growth, and myocyte necrosis and apoptosis. Thus, therapy of heart failure should consist of pharmacologic agents not only to relieve **symptoms** but also to prevent and attenuate ventricular remodeling and progressive heart failure, thereby improving prognosis. In patients who are symptomatic, ACE inhibitors along with digitalis and diuretics as initial therapy (triple therapy) have the greater potential to improve exercise tolerance and decrease the incidence of **treatment** failure compared with diuretics alone or a combination of diuretics and digitalis. Diuretics alone should not be considered for long-term therapy as plasma renin activity, angiotensin II, aldosterone, norepinephrine and **vasopressin levels** may increase. ACE inhibitors decrease mortality in patients with heart failure resulting from left ventricular systolic dysfunction. The results of presently available studies indicate that angiotensin II receptor blockers (ARBs) do not provide any advantage over ACE inhibitors regarding survival benefit but may be better tolerated. Long-term adrenergic inhibition with the use of ss-adrenoceptor antagonists added to ACE inhibitors is associated with attenuation of ventricular remodeling, improvement in ventricular function and clinical class and survival of patients with symptomatic systolic left ventricular failure. Thus, initial pharmacotherapy for systolic heart failure should consist of: maximal tolerated dosages of ACE inhibitors;ARBs if ACE inhibitors are not tolerated because of intractable cough or angioedema;adequate dosages of hydralazine and isosorbide dinitrate if ACE inhibitors or ARBs are not tolerated; relatively low dosages of digoxin (serum concentrations of < or = 1.0 ng/dl) if not contraindicated; and diuretics to relieve congestive **symptoms**. Addition of spironolactone to ACE inhibitors can result in a significant reduction in the risk of sudden death in patients with symptomatic severe heart failure. Myocardial infarction resulting from ischemic heart disease is the most common cause of systolic left ventricular failure and the therapeutic modalities with potential to reduce the risks of myocardial infraction, such as risk factor modification, adequate control of diabetes and hypertension, antiplatelet agents and lipid-lowering agents, should also be included in the initial therapy.

L26 ANSWER 3 OF 4 MEDLINE on STN DUPLICATE 2

97202505. PubMed ID: 9050024. The role of vasopressin on the effect of U-50,488 to block the development of morphine tolerance and physical dependence. Tao P L; Liu W C; Tsuei Y S; Cheng C Y. (Department of Pharmacology, National Defense Medical Center, Taipei, Taiwan, R.O.C.) Naunyn-Schmiedeberg's archives of pharmacology, (1997 Feb) 355 (2) 281-7. Journal code: 0326264. ISSN: 0028-1298. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.

AB U-50,488, a selective kappa-opioid receptor agonist, has been reported to inhibit the development of antinociceptive tolerance to morphine in mice, rats and guinea pigs, but the mechanism involved in this action remains unknown. Since U-50,488 has been reported to suppress the plasma **vasopressin level**, we investigated the role of

morphine tolerance and dependence. We found that coadministration of 8 mg/kg U-50,488 (i.p.) with morphine almost completely block morphine tolerance and partially block withdrawal **symptoms**. In contrast, coadministration of AVP (0.3 microgram/kg, i.p., or 0.01 microgram, i.c.v.) with morphine and U-50,488, the effects of U-50,488 to block morphine tolerance and dependence were reversed. In addition, **treatment** of AVP antagonist (dPTyr(Me)AVP, 0.5 microgram/kg, i.p. or 0.5 microgram, i.c.v.) has the similar effect as U-50,488 to block morphine tolerance. In summary, the effect of U-50,488 to block morphine tolerance and dependence may relate to its inhibitory effect on AVP release.

L26 ANSWER 4 OF 4 MEDLINE on STN DUPLICATE 3
93002798. PubMed ID: 1390475. Stimulation of vasopressin release in women with primary dysmenorrhoea and after oral contraceptive **treatment** --effect on uterine contractility. Ekstrom P; Akerlund M; Forsling M; Kindahl H; Laudanski T; Mrugacz G. (Department of Obstetrics and Gynecology, University Hospital, Lund, Sweden.) British journal of obstetrics and gynaecology, (1992 Aug) 99 (8) 680-4. Journal code: 7503752. ISSN: 0306-5456. Pub. country: ENGLAND: United Kingdom. Language: English.

AB OBJECTIVE: To study aspects of the aetiology of primary dysmenorrhoea and mechanisms underlying the therapeutic effect in this condition of an oral contraceptive. INTERVENTION: Intrauterine pressure was recorded before and during infusion of hypertonic saline (5% NaCl, 0.06 ml/kg/min) over 75 min on the first day of bleeding in women with dysmenorrhoea and after 3 weeks of oral contraceptive **treatment**. Plasma sampling every 15 min of ongoing infusion for the estimation of osmolality, arginine vasopressin, oxytocin and the prostaglandin (PG) F-metabolite, 15-keto-13,14-dihydro-PGF2 alpha. SUBJECTS: Ten healthy nulliparous women with moderate to severe primary dysmenorrhoea. MAIN OUTCOME MEASURES: Plasma levels of posterior pituitary hormones and the PGF-metabolite. Total pressure area (TPA) of the recording curve. RESULTS: In dysmenorrhoea before infusion the plasma concentration of vasopressin was in mean 2.18, oxytocin 5.05 and the PGF-metabolite 321.5 pmol/l, and the TPA 3.8 kPa x 10 min. After oral contraceptive **treatment** the **vasopressin level** and the TPA were significantly reduced. At both sessions apart from intensifying the pain, the saline infusion increased vasopressin and oxytocin levels as well as the TPA, whereas the concentration of the PGF-metabolite at both sessions decreased. CONCLUSION: Confirmation is provided of the elevated secretion of arginine vasopressin and PGF2 alpha, as well as increased uterine activity in primary dysmenorrhoea. The observations are in agreement with the concept that a lowered level of vasopressin and a decreased uterine activity contributes to the beneficial effect of OCs in the condition. Stimulation of the secretion of vasopressin increases the uterine activity and **symptoms** of primary dysmenorrhoea, but results suggest that this effect does not involve a mechanism of increased PGF-synthesis. The role of oxytocin in dysmenorrhoea can not yet be defined.

=> s polyuria treatment
L27 9 POLYURIA TREATMENT

=> s l27 and vasopressin
L28 4 L27 AND VASOPRESSIN

L29 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2004 ACS on STN
2002:10446 Document No. 136:69828 Preparation of fused azepine derivatives and their use as antidiuretic agents. Ashworth, Doreen Mary; Pitt, Gary Robert William; Hudson, Peter; Yea, Christopher Martyn; Franklin, Richard Jeremy; Semple, Graeme (Ferring B.V., Neth.). PCT Int. Appl. WO 2002000626 A1 20020103, 107 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-GB2737 20010621. PRIORITY: GB 2000-15601 20000626.

GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Compds. according to general formulas [I and II; W = N or C-R4; R1-R4 = H, F, Cl, Br, alkyl, CF3, Ph, OH, alkoxy, NH2, NH-alkyl, N(alkyl)2, NO2, cyano, or R2 and R3 together can be CH:CHCH:CH; G1 = a bicyclic or tricyclic fused azepine derivative selected from Q - Q5 [wherein A1, A4, A7, A10 = CH2, O and NR5; A2, A3, A9, A11, A13, A14, A15 = CH and N; either A5 is a covalent bond and A6 is S, or A5 is N:CH and A6 is a covalent bond; A8, A12 = NH, NMe, S; A16, A17 = CH2, or one of A16 and A17 is CH2 and the other is selected from CH(OH), CF2, O, S, SO, SO2, and NR5 (wherein R5 is selected from H, alkyl, CO-alkyl and (CH2)1-4-R6; R6 = Ph, pyridyl, OH, alkoxy, NH2, NH-alkyl, N(alkyl)2, NO2, CO2H, cyano); Y = CH or N; Z = CH:CH, S]; G2 = Ar(CH2)c(SO2)d[NHC(:V)]e, R7(CH2)f-D-C(:V), Q6 [wherein Ar = (un)substituted Ph or pyridyl, naphthyl; D = a covalent bond, NH; V = O, C-CN, S; E1, E2 = H, OMe or F, or one of E1 and E2 is OH, O-alkyl, OBn, OPh, OAc, F, Cl, Br, N3, NH2, NHBn or NHAc and the other is H, or E1 and E2 together are O, O(CH2)gO or S(CH2)gS; F1, F2 = H, or together are O or S; L = OH, alkoxy, NH2, NH-alkyl and NR9R10; R7 = H, alkyl, alkenyl and COR8 (R8 = OH, alkoxy, NH2, NH-alkyl, N(alkyl)2, pyrrolidinyl and piperidinyl); R9 and R10 are both alkyl, or together are (CH2)h or (CH2)2O(CH2)2; c,d,e = 0,1; f = 0-4; g = 2,3; h = 3-5, provided that d and e are not both 0]] are prepared Thses compds. are **vasopressin** V2 receptor agonists and are useful for the treatment of nocturnal enuresis, nocturia, polyuria resulting from central diabetes insipidus, urinary incontinence or bleeding disorders. Thus, 1-[4-(aminomethyl)-3-methylbenzoyl]-2,3,4,5-tetrahydro-1H-benzo[b]azepine hydrochloride (preparation given) was stirred with diisopropylethylamine and carbonyl diimidazole in DMF at room temperature for 40 min and condensed with L-proline-N,N-dimethylamide to give 1-[2-Methyl-4-(2,3,4,5-tetrahydro-1-benzazepin-1-ylcarbonyl)benzylcarbamoyl]-L-proline-N,N-dimethylamide (III). III and 4-methoxy-1-[2-chloro-4-(2,3,4,5-tetrahydrothieno[3,2-b]azepin-1-ylcarbonyl)benzylcarbamoyl]-proline-N,N-dimethylamide at 10 mg/kg/ p.o. inhibited the urine output by 82 and 90%, resp., in Brattleboro rats. A tablet formulation containing III was prepared

L29 ANSWER 2 OF 3 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.

ISSN: 1362-4393. CODEN: SPCOFM. Pub. Country: United Kingdom. Language: English. Summary Language: English.

AB Introduction: Healthy individuals have a nocturnal decrease in urine output due to increased plasma antidiuretic hormone levels at night. This does not occur in spinal cord injury and most patients experience nocturnal polyuria, which triggers dysreflexic crises secondary to urinary bladder overdistension, and interferes with patients' sleep due to the need for extra catheterization. Objective: To evaluate the diurnal variation in ADH level, urinary output, and plasma and urine osmolality in SCI patients with regard to their level of injury and in comparison with age- and sex-matched healthy individuals. Materials and methods: Sixteen ASIA-A spinal cord-injured patients, eight with paraplegia, eight with tetraplegia, and eight healthy individuals, were evaluated for urinary output, urine and serum osmolality, and antidiuretic hormone levels during day and night hours. Results: Absence of diurnal variation in urinary output and antidiuretic hormone secretion was detected in both paraplegic and tetraplegic patients, while antidiuretic hormone levels rose significantly at night in the control group. Conclusion: Antidiuretic hormone levels should be monitored both day and night in spinal cord injury patients with severe nocturnal **polyuria**.
Treatment with desaminocystein-D-arginine **vasopressin** can be attempted when conservative measures fail to control nocturnal polyuria, especially in patients who are on an intermittent catheterization program.

L29 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2004 ACS on STN

1980:191799 Document No. 92:191799 DDAVP (1-desamino-8-D-arginine-**vasopressin**) treatment of lithium-induced polyuria in the rat. Christensen, Sten (Dep. Pharmacol., Univ. Copenhagen, Copenhagen, DK-2100, Den.). Scandinavian Journal of Clinical and Laboratory Investigation, 40(2), 151-7 (English) 1980. CODEN: SJCLAY. ISSN: 0036-5513.

AB The antidiuretic responses of arginine **vasopressin** (AVP) [113-79-1] and DDAVP [16679-58-6] were studied in rats with marked polyuria (.apprx.100 mL/100 g/24 h) induced by administration of Li to the diet for 3-4 mo. The hormones were infused i.v. and s.c. at a constant rate for 7 days using implantable osmotic minipumps. Body weight, food consumption, and urine volume and osmolality were recorded daily. Whereas supramaximal doses of AVPhad little effect on spontaneous urine flow and osmolality, DDAVP (0.1 μg/h, i.v. or 1 μg/h, s.c.) restored urine volume and osmolality to near-normal values. The reversibility of Li-induced impairment of renal concentrating ability caused by excessive hormonal stimulation is not immediately compatible with the recent hypothesis that Li-polyuria may reflect irreversible structural kidney damage.

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=> s hyperosmolarity treatment
L30           0 HYPEROSMOLARITY TREATMENT

=> s hyperosmolarity
L31        4102 HYPEROSMOLARITY

=> s l31 and decrease vasopressin
L32           0 L31 AND DECREASE VASOPRESSIN

=> s l31 and treatment
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=> dup remove l34
PROCESSING COMPLETED FOR L34
L36 22 DUP REMOVE L34 (12 DUPLICATES REMOVED)

=> d l36 1-22 cbib abs

L36 ANSWER 1 OF 22 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
2003431703 EMBASE [Diabetes in the elderly]. LE DIABETE DU SUJET AGE. Bringer J.. J. Bringer, Service des Maladies Endocriniennes, Hopital Lapeyronie, CHRU Montpellier, 371, avenue Doyen Gaston Giraud, 34000 Montpellier, France. Annales d'Endocrinologie 64/4 (354-356) 2003.
Refs: 10.
ISSN: 0003-4266. CODEN: ANENAG. Pub. Country: France. Language: French.

L36 ANSWER 2 OF 22 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
2003199703 EMBASE Ligand-induced μ opioid receptor endocytosis and recycling in enteric neurons. Minnis J.G.; Patierno S.; Kohlmeier S.E.; Brecha N.C.; Tonini M.; Sternini C.. C. Sternini, CURE Digest. Dis. Research Center, Building 115, Vet. Admin. Gtr. Los Angeles H., 11301 Wilshire Boulevard, Los Angeles, CA 90073, United States. csternin@ucla.edu. Neuroscience 119/1 (33-42) 18 Jun 2003.
Refs: 55.
ISSN: 0306-4522. CODEN: NRSCDN. Pub. Country: United Kingdom. Language: English. Summary Language: English.
AB Immunohistochemistry and confocal microscopy were used to investigate endocytosis and recycling of the native μ opioid receptor (μOR) in enteric neurons. Isolated segments of the guinea-pig ileum were exposed to increasing concentrations of μOR agonists at 4°C to allow ligand binding and warming to 37°C for 0 min (baseline) to 6 h in ligand-free medium to allow receptor internalization and recycling. The endogenous ligand, [Met]enkephalin, and [D-Ala(2),MePhe(4),Gly-ol(5)] enkephalin (DAMGO), an opioid analog, and the alkaloids, etorphine and fentanyl, induced rapid internalization of μOR immunoreactivity in enteric neurons, whereas morphine did not. μOR internalization was prevented by μOR **antagonists**. Basal levels of μOR immunoreactivity in the cytoplasm were 10.52±2.05%. DAMGO (1 nM-100 μM) induced a concentration-dependent increase of μOR immunofluorescence density in the cytoplasm to a maximum of 84.37±2.26%. Translocation of μOR immunoreactivity in the cytoplasm was detected at 2 min, reached the maximum at 15-30 min, remained at similar levels for 2 h, began decreasing at 4 h, and was at baseline values at 6 h. A second exposure to DAMGO (100 nM) following recovery of internalized μOR immunoreactivity at the cell surface induced a translocation of μOR immunoreactivity in the cytoplasm comparable to the one observed following the first exposure (46.89±3.11% versus 43.31±3.80%). μOR internalization was prevented by hyperosmolar sucrose, phenylarsine oxide or potassium depletion, which inhibit clathrin-mediated endocytosis. μOR recycling was prevented by pre-**treatment** with bafilomycin A1, an acidotropic agent that inhibits endosomal acidification, but not by the protein synthesis inhibitor, cycloheximide. This study shows that native μOR in enteric neurons undergoes ligand-selective endocytosis, which is primarily clathrin-mediated, and recycles following endosomal acidification.

P.M.; Parab P.V.. Dr. P.M. Dalal, Municipal Bldg. No. 3, Clark Road, Haji Ali, Mumbai 400 034, India. pmdalal@vsnl.net. Neurology India 50/4 (380-385) 2002.
Refs: 42.
ISSN: 0028-3886. CODEN: NURYAY. Pub. Country: India. Language: English. Summary Language: English.

AB Incidence of CVD in diabetic men was reported to be twice as that of non-diabetics and almost three times greater in diabetic women in the Framingham Study. It is postulated that excessive glycation and oxidation, endothelial dysfunction and increased platelet aggregation may be responsible for endothelial proliferation and thickening of plasmatic membrane in small blood vessels ('lipohyalinosis') leading to lacunar infarction. Prothrombotic state may precipitate a stroke, however, platelet aggregability, elevated fibrinopeptide A (FPA) and D-dimer were not significantly related to stroke in diabetic mellitus (DM), whereas suppressed fibrinolytic activity was a common finding. Of many unknown factors in pathogenesis, the deficient insulin secretion, resistance to action of insulin at level of 'insulin receptors', changes in counter regulatory hormones (e.g. glucagon, pancreatic polypeptides, growth hormone, catecholamines, etc.) and decrease in the hepatic sensitivity to insulin action in suppressing glucose output have received more attention. Hyperosmolar state can simulate stroke syndromes. Early recognition and **treatment** of risk factor such as hypertension or better glycemic control, correlation of hyperlipidemia or obesity in diabetic population are important. In diabetic subjects already showing recurrent transient cerebral ischemic attacks (TIAs) or minor strokes, the benefit of antiplatelet agents or antithrombotic therapy in prevention of major strokes is well established. Ramipril has been found to be effective in reducing stroke risk by 33% in diabetic patients in HOPE study.

L36 ANSWER 4 OF 22 MEDLINE on STN

2002312687. PubMed ID: 12054469. Expression and regulation of the Na(+)/K(+)/2Cl(-) cotransporter NKCC1 in rat liver and human HuH-7 hepatoma cells. Schliess Freimut; Schafer Christine; vom Dahl Stephan; Fischer Richard; Lordnejad Mohammad R; Haussinger Dieter. (Clinic for Gastroenterology, Hepatology and Infectiology, Heinrich-Heine-University, D-40225 Dusseldorf, Germany.) Archives of biochemistry and biophysics, (2002 May 15) 401 (2) 187-97. Journal code: 0372430. ISSN: 0003-9861. Pub. country: United States. Language: English.

AB The expression of sodium potassium chloride cotransporter 1 (NKCC1) was studied in different liver cell types. NKCC1 was found in rat liver parenchymal and sinusoidal endothelial cells and in human HuH-7 hepatoma cells. NKCC1 expression in rat hepatic stellate cells increased during culture-induced transformation in the myofibroblast-like phenotype. NKCC1 inhibition by bumetanide increased alpha(1)-smooth muscle actin expression in 2-day-cultured hepatic stellate cells but was without effect on basal and platelet-derived-growth-factor-induced proliferation of the 14-day-old cells. In perfused rat liver the NKCC1 made a major contribution to volume-regulatory K(+) uptake induced by **hyperosmolarity**. Long-term hyperosmotic **treatment** of HuH-7 cells by elevation of extracellular NaCl or raffinose concentration but not hyperosmotic urea or mannitol profoundly induced NKCC1 mRNA and protein expression. This was antagonized by the compatible organic osmolytes betaine or taurine. The data suggest a role of NKCC1 in stellate cell transformation, hepatic volume regulation, and long-term adaption to dehydrating conditions. (c) 2002 Elsevier Science (USA).

Reservoir Road NW, Washington, DC 20007, USA
verbalis@georgetown.edu. Pituitary 5/2 (119-132) 2002.
Refs: 37.
ISSN: 1386-341X. CODEN: PITUF. Pub. Country: United States. Language: English. Summary Language: English.

AB Disorders of body fluids, notably central diabetes insipidus (CDI) and the syndrome of inappropriate antidiuretic hormone secretion (SIADH), are relatively uncommon as a presenting symptom of sellar and suprasellar masses, but quite common following surgical resection of such lesions. It therefore behooves clinicians treating such patients to have a good understanding of the pathophysiology, the differential diagnosis and the management of these disorders. This review discusses some general issues concerning the pathogenesis, differential diagnosis, clinical manifestations and therapy of hyperosmolar and hypoosmolar syndromes, including CDI and SIADH, and then more specifically addresses the evaluation and **treatment** of pre- and postoperative disorders of water metabolism in patients with pituitary adenomas.

L36 ANSWER 6 OF 22 MEDLINE on STN

2002183999. PubMed ID: 11909643. Activation of NKCC1 by hyperosmotic stress in human tracheal epithelial cells involves PKC-delta and ERK. Liedtke Carole M; Cole Thomas S. (Cystic Fibrosis Center, Departments of Pediatrics, and Physiology and Biophysics, Pediatric Pulmonology, Case Western Reserve University, BRB, Room 824, 2109 Adelbert Rd., Cleveland, OH 44106-4948, USA.. cx17@po.cwru.edu) . Biochimica et biophysica acta, (2002 Feb 13) 1589 (1) 77-88. Journal code: 0217513. ISSN: 0006-3002. Pub. country: Netherlands. Language: English.

AB Hyperosmotic stress activates Na+-K+-2Cl- cotransport (NKCC1) in secretory epithelia of the airways. NKCC1 activation was studied as uptake of 36Cl or 86Rb in human tracheal epithelial cells (HTEC). Application of hypertonic sucrose or NaCl increased bumetanide-sensitive ion uptake but did not affect Na+/H+ and Cl-/OH-(HCO3-) exchange carriers. **Hyperosmolarity** decreased intracellular volume (Vi) after 10 min from 7.8 to 5.4 microl/mg protein and increased intracellular Cl- (Cl-i) from 353 to 532 nmol/mg protein. **Treatment** with an alpha-adrenergic agent rapidly increased Cl-i and Vi in a bumetanide-sensitive manner, indicating uptake of ions by NKCC1 followed by osmotically obligated water. These results indicate that HTEC act as osmometers but lose intracellular water slowly. Hyperosmotic stress also increased the activity of PKC-delta and of the extracellular signal-regulated kinase ERK subgroup of the MAPK family. Activity of stress-activated protein kinase JNK was not affected by **hyperosmolarity**. PD-98059, an inhibitor of the ERK cascade, reduced ERK activity and bumetanide-sensitive 36Cl uptake. PKC inhibitors blocked activation of ERK indicating that PKC may be a downstream activator of ERK. The results indicate that hyperosmotic stress activates NKCC1 and this activation is regulated by PKC-delta and ERK.

L36 ANSWER 7 OF 22 MEDLINE on STN

2001420245. PubMed ID: 11467861. Dissociation of 5' AMP-activated protein kinase activation and glucose uptake stimulation by mitochondrial uncoupling and hyperosmolar stress: differential sensitivities to intracellular Ca2+ and protein kinase C inhibition. Patel N; Khayat Z A; Ruderman N B; Klip A. (Programme in Cell Biology, The Hospital for Sick Children, Toronto, Ontario, M5G 1X8, Canada.) Biochemical and biophysical research communications, (2001 Jul 27) 285 (4) 1066-70. Journal code: 0372516. ISSN: 0006-291X. Pub. country: United States. Language: English.

mechanism. Recently, 5' AMP-activated protein kinase (AMPK) has been proposed to mediate the stimulation of glucose uptake by energy stressors such as exercise and hypoxia. Changes in Ca2+ and cPKC have also been invoked in the stimulation of glucose uptake by exercise and hypoxia. Here we examine whether changes in cytosolic Ca2+ or cPKC lead to activation of AMPK. We show that **treatment** of L6 cells with DNP (0.5 mM) or hyperosmolar stress (mannitol, 0.6 M) increased AMPK activity by 3.5-fold. AMPK activation peaked by 10-15 min prior to maximal stimulation of glucose uptake. Intracellular Ca2+ chelation and cPKC inhibition prior to **treatment** with DNP and **hyperosmolarity** significantly reduced cell surface GLUT4 levels and hexose uptake but had no effect on AMPK activation. These results illustrate a break in the relationship between AMPK activation and glucose uptake in skeletal muscle cells. Activation of AMPK does not suffice to stimulate glucose uptake in response to DNP and **hyperosmolarity**. Copyright 2001 Academic Press.

L36 ANSWER 8 OF 22 MEDLINE on STN

2001488655. PubMed ID: 11530937. Insulin resistance induced by loop diuretics and **hyperosmolarity** in perfused rat liver. Schliess F; von Dahl S; Haussinger D. (Clinic for Gastroenterology, Hepatology and Infectiology, Heinrich-Heine-University, Dusseldorf, Germany.) Biological chemistry, (2001 Jul) 382 (7) 1063-9. Journal code: 9700112. ISSN: 1431-6730. Pub. country: Germany: Germany, Federal Republic of. Language: English.

AB Insulin-induced cell swelling was recently suggested to reflect an independent signal for metabolic insulin effects such as inhibition of hepatic proteolysis, which is transmitted at the level of autophagosome formation via p38MAPK activation [Haussinger et al., Gastroenterology 116 (1999), 921-935]. Here, the role of insulin-induced cell swelling in the overall context of insulin signalling towards proteolysis inhibition was studied in perfused rat liver. Loop diuretics and **hyperosmolarity**, which impair insulin-stimulated cell swelling, strongly blunt Erk-2 and p38MAPK activation as well as proteolysis inhibition by insulin, but are without effect on insulin-induced tyrosine phosphorylation of IR-beta and IRS-1. Inhibitors of phosphatidylinositol-3-kinase (PI3-kinase) also block insulin-induced cell swelling, MAP kinase activation and proteolysis inhibition, but the antiproteolytic response to hypoosmolarity remains unaffected. We suggest that PI3-kinase-mediated cell swelling induced by insulin is required to amplify the insulin signal to MAP kinases and thus proteolysis regulation. The perturbation of insulin-induced cell swelling may be of pathophysiological relevance for the development of insulin resistance in clinical situations associated with hyperosmotic dehydration and loop diuretic **treatment**.

L36 ANSWER 9 OF 22 CAPLUS COPYRIGHT 2004 ACS on STN

2000:304164 Document No. 133:217605 Local injection of pertussis toxin attenuates morphine withdrawal excitation of rat supraoptic nucleus neurones. Brown, C. H.; Johnstone, L. E.; Murphy, N. P.; Leng, G.; Russell, J. A. (Department of Biomedical Sciences, University Medical School, Edinburgh, UK). Brain Research Bulletin, 52(2), 115-121 (English) 2000. CODEN: BRBUDU. ISSN: 0361-9230. Publisher: Elsevier Science Inc..

AB Morphine inhibits oxytocin neurons via Gi/0-protein-linked μ-opioid receptors. Following chronic morphine administration oxytocin cells develop dependence, shown by withdrawal excitation after administration of the opioid **antagonist**, naloxone. Here, inactivation of

either systemic cholecystokinin administration or systemic hypertonic saline administration, indicating that pertussis toxin does not prevent oxytocin cells from responding to stimuli that are not mediated by Gi/0-proteins. Finally, pertussis toxin reduced acute morphine inhibition of systemic hypertonic saline-induced Fos protein expression in the supraoptic nucleus, confirming that pertussis toxin effectively inactivates Gi/0-proteins in the supraoptic nucleus. Thus, the expression of morphine withdrawal excitation by supraoptic nucleus oxytocin cells requires the functional integrity of Gi/0-proteins within the nucleus.

L36 ANSWER 10 OF 22 MEDLINE on STN

1999126691. PubMed ID: 9927384. **Hyperosmolarity**-induced interleukin-8 expression in human bronchial epithelial cells through p38 mitogen-activated protein kinase. Hashimoto S; Matsumoto K; Gon Y; Nakayama T; Takeshita I; Horie T. (First Department of Internal Medicine, Nihon University School of Medicine, Tokyo, Japan.) American journal of respiratory and critical care medicine, (1999 Feb) 159 (2) 634-40. Journal code: 9421642. ISSN: 1073-449X. Pub. country: United States. Language: English.

AB The changes in airway osmolarity have been described to contribute to the production of exercise- induced bronchoconstriction (EIB) and the development of the late-phase response (LPR). The mechanism has been investigated; however, the responsiveness of bronchial epithelial cells (BEC) to **hyperosmolarity** and the intracellular signals leading to cell activation have not been determined. In this study, we examined the effect of hyperosmolar medium on interleukin-8 (IL-8) expression and the role of p38 mitogen-activated protein (MAP) kinase and c-Jun NH2 terminal kinase (JNK) in human BEC in this response in order to clarify the intracellular signals regulating IL-8 expression in **hyperosmolarity**-stimulated BEC. The results showed that **hyperosmolarity** induced IL-8 expression in a concentration dependent manner, p38 MAP kinase phosphorylation and activation, and JNK activation whether NaCl or mannitol was used as the solute. SB 203580 as the specific p38 MAP kinase inhibitor inhibited **hyperosmolarity** -induced p38 MAP kinase activation and partially inhibited **hyperosmolarity**-induced IL-8 expression. These results indicate that p38 MAP kinase, at least in part, regulates **hyperosmolarity** -induced IL-8 expression in BEC. However, other signals such as JNK are possibly also involved. These results provide new evidence on the mechanism responsible for the development of the LPR induced by EIB, and a strategy for **treatment** with the specific p38 MAP kinase inhibitor.

L36 ANSWER 11 OF 22 MEDLINE on STN

1999311964. PubMed ID: 10385238. **Hyperosmolarity** reduces the relaxing potency of nitric oxide donors in guinea-pig trachea. Hjoberg J; Hogman M; Hedenstierna G. (Department of Medical Sciences, Clinical Physiology, Uppsala University, University Hospital, Sweden.. josephine.hjoberg@klinfys.uu.se) . British journal of pharmacology, (1999 May) 127 (2) 391-6. Journal code: 7502536. ISSN: 0007-1188. Pub. country: ENGLAND: United Kingdom. Language: English.

AB 1. Non-responders to inhaled nitric oxide **treatment** have been observed in various patient groups. The bronchodilatory effect of inhaled nitric oxide was attenuated when the airway lumen was rendered hyperosmolar in an in vivo study on rabbits. We used a guinea-pig tracheal perfusion model to investigate the effects of increased

contracted to the same extent under anisosmotic [illegible]
the untreated trachea was completely relaxed by SNP but, after hyperosmolar pretreatment, SNP could no longer relax the trachea. 3. SNAP relaxed the CCh contracted trachea by 27+/-5%. After pretreatment with intraluminal **hyperosmolarity**, SNAP relaxed the trachea by 11+/-4%, which was less than in the iso-osmolar control ($P<0.05$). 4. Extraluminal **hyperosmolarity** did not affect carbachol elicited contraction, and SNP administered externally during extraluminal **hyperosmolarity** was able to relax the trachea ($P<0.05$). 5. The cell permeable guanosine 3'5'-cyclic monophosphate analogue 8-Br-cGMP relaxed the CCh contracted trachea in both iso-osmolar ($P<0.05$) and hyperosmolar conditions ($P<0.05$). 6. The relaxant effect of nitric oxide donors on tracheal smooth muscle is markedly reduced when the airway epithelium is exposed to hyperosmolar solution.

L36 ANSWER 12 OF 22 MEDLINE on STN DUPLICATE 1

1999255949. PubMed ID: 10322639. Developmental expression of urine concentration-associated genes and their altered expression in murine infantile-type polycystic kidney disease. Gattone V H 2nd; Maser R L; Tian C; Rosenberg J M; Branden M G. (Department of Anatomy and Cell Biology, University of Kansas Medical Center, Kansas City 66160-7400, USA.. vgattone@kumc.edu) . Developmental genetics, (1999) 24 (3-4) 309-18. Journal code: 7909963. ISSN: 0192-253X. Pub. country: United States. Language: English.

AB Currently, there is little understanding of what factors regulate the development of urine concentrating capability in normal or polycystic kidney. The present study examined the developmental expression of genes associated with urine concentration in developing mice, including C57BL/6J-cpk/cpk mice with autosomal recessive-infantile (AR) polycystic kidney disease (PKD). Concentration of urine requires: 1) medullary collecting ducts (CD) located within a hypertonic interstitium, 2) CD cell expression of functional arginine vasopressin V2 receptors (AVP-V2R), and 3) the presence of appropriate CD water channels (aquaporins, AQP 2 and 3). An increase in urine osmolarity, normally seen between 1 and 3 weeks of age, was absent in cpk cystic mice. Aldose reductase mRNA expression (a gene upregulated by medullary **hyperosmolarity**) increased in normal mice, but remained low in the cystic kidney, suggesting the absence of a hypertonic medullary interstitium. AVP-V2R, AQP2, and AQP3 mRNA expression normally increase between 7 and 14 days. However, all were dramatically overexpressed even at 7 days of age in the cpk kidney in vivo, but decreased in vitro. Activation of the AVP-V2 receptor stimulates the production of cAMP, a substance known to promote cyst enlargement. To determine if CD cAMP, generated from increased AVP-V2Rs, was accelerating the PKD, cystic mice and their normal littermates were treated with OPC31260, a relatively specific AVP-V2R **antagonist**. OPC31260 **treatment** of cystic mice led to an amelioration of the cystic enlargement and azotemia. **Treatment** also decreased renal AQP2 mRNA but increased AVP-V2R and AQP3 mRNA expression in vivo. AVP upregulates the expression of AVP-V2R, AQP2, and AQP3 mRNAs in vitro. Renal EGF, known to inhibit AVP-V2R activity, downregulates AVP-V2R mRNA in vitro. Brief in vivo EGF **treatment**, known to decrease PKD in cpk mice, led to increased expression of AVP-V2R, AQP2, and AQP3 mRNAs at 2 weeks in both normal and cystic mice but no change was evident at 3 weeks of age. In conclusion, the development of urinary concentration ability correlates with the development of an increased medullary osmotic gradient which is diminished in murine ARPKD. However, CD genes associated with this process are overexpressed in vivo but underexpressed

induces spreading depression-like depolarization in hippocampal slices. Balestrino M; Young J; Aitken P. (Department of Neurological Sciences, University of Genova, Via De Toni 5, 16132, Genova GE, Italy.. research@csita.unige.it) . Brain research, (1999 Aug 14) 838 (1-2) 37-44. Journal code: 0045503. ISSN: 0006-8993. Pub. country: Netherlands. Language: English.

AB We used ouabain (100 microM) to block Na+,K(+)ATPase of in vitro rat hippocampal slices. This **treatment** was sufficient to cause the sudden depolarization that is the hallmark of both spreading depression (SD) and of the SD-like anoxic depolarization (AD). This depolarization was accompanied by a large and sudden increase in [K](o), also reminiscent of that observed during both SD and AD. Ouabain-induced SD did not require a complete inactivation of Na+,K(+)ATPase, as it occurred when the enzyme was still capable of providing recovery of both V(o) and [K](o). The data indicate that functional inactivation of Na+,K(+)ATPase per se initiates events that lead to an SD-like AD. This ouabain-induced depolarization was not affected by block of synaptic transmission, instead it was abolished by **hyperosmolarity** of the extracellular space. The possible relevance of these findings to the pathophysiology of AD is discussed.

L36 ANSWER 14 OF 22 MEDLINE on STN DUPLICATE 2

1998446579. PubMed ID: 9773402. Effects of estrogen on tight junctional resistance in cultured human umbilical vein endothelial cells. Cho M M; Ziats N P; Abdul-Karim F W; Pal D; Goldfarb J; Utian W H; Gorodeski G I. (Department of Reproductive Biology, Case Western Reserve University School of Medicine, Cleveland, Ohio, USA.) Journal of the Society for Gynecologic Investigation, (1998 Sep-Oct) 5 (5) 260-70. Journal code: 9433806. ISSN: 1071-5576. Pub. country: United States. Language: English.

AB OBJECTIVE: To study the effects of estrogen on transendothelial paracellular permeability in women. METHODS: Human umbilical vein endothelial cells (HUVEC) obtained from women were grown on filters. The paracellular permeability characteristics were determined in terms of changes in the permeability to the polar acid pyranine (Ppyr) and as changes in the transendothelial electrical resistance (RTE). Tight junctional resistance characteristics were assayed by lowering luminal NaCl and measuring the dilution potential, and were expressed as the ratio of monoion mobility uCl/uNa (cation selectivity). RESULTS: Low extracellular calcium and **hyperosmolarity** increased Ppyr and decreased RTE. The former but not the latter condition abolished the endothelium-specific cation selectivity. **Treatment** with 10 nM of estradiol-17 beta had no effect on RTE, but it increased the cation selectivity. The effect of estradiol required 1-6 hours' incubation with the hormone; it was dose dependent and saturable, with a median effective concentration of estradiol of 1 nM. Diethylstilbestrol, but not estriol, could mimic the effect of estradiol, and the estrogen receptor **antagonist** ICI-182, 780 blocked it. CONCLUSION: Cultured HUVEC cells form patent tight junctions. Estrogens increase the cation selectivity across HUVEC cultures. The effect of estrogen may be mediated by an estrogen receptor. These effects may be important for vasculoprotection in cases of sudden changes in ions levels across the capillary wall, such as ischemia or reperfusion.

L36 ANSWER 15 OF 22 MEDLINE on STN

97396290. PubMed ID: 9252481. Glucose transporter expression in L6 muscle [illegible] and stress-activated pathways. Taha C;

2,4 dinitrophenol (DNP, an uncoupler of [illegible]
increases energy demand) and 300 mM mannitol (**hyperosmolarity**) on glucose transporter (GLUT) expression in L6 muscle cells and the signaling pathways involved. We found the following. 1) The insulin-mediated increase in GLUT-1 is 70-kDa ribosomal protein S6 kinase (p70 S6 kinase) and p38 mitogen-activated protein kinase (MAPK) dependent but extracellular signal-regulated protein kinase (ERK) and MAPK/ERK kinase (MEK) independent. The hypertonicity-stimulated elevation in GLUT-1 is p70 S6 kinase, p38 MAPK, and MEK dependent yet ERK independent. DNP also increased GLUT-1 protein but did not depend on any of the above pathways, 2) Insulin increased GLUT-3 protein in a p70 S6 kinase-independent but MEK/ERK-dependent fashion. Inhibition of p38 MAPK potentiated the effect of insulin on GLUT-3. Hypertonicity increased GLUT-3 via p70 S6 kinase- and p38 MAPK-dependent pathways. In conclusion, we have dissected the molecular mechanisms used by insulin and hypertonicity that culminate in the induction of GLUT-1 and GLUT-3. The mechanism(s) used by DNP remains unknown.

L36 ANSWER 16 OF 22 MEDLINE on STN

96077136. PubMed ID: 7492303. **Hyperosmolarity** stimulates prostaglandin synthesis and cyclooxygenase-2 expression in activated rat liver macrophages. Zhang F; Warskulat U; Wettstein M; Schreiber R; Henninger H P; Decker K; Haussinger D. (Medizinische Universitatsklinik, Heinrich-Heine-Universitat, Dusseldorf, Germany.) Biochemical journal, (1995 Nov 15) 312 (Pt 1) 135-43. Journal code: 2984726R. ISSN: 0264-6021. Pub. country: ENGLAND: United Kingdom. Language: English.

AB The effect of aniso-osmotic exposure on the level of inducible cyclooxygenase (Cox-2) and on prostanoid synthesis was studied in cultured rat liver macrophages (Kupffer cells). In lipopolysaccharide (LPS)- or phorbol 12-myristate 13-acetate-stimulated Kupffer cells, hyperosmotic (355 mosmol/l) exposure, due to addition of NaCl or impermeant sugars, markedly increased prostaglandin (PG) E2, D2 and thromboxane B2 synthesis in a time- and osmolarity-dependent manner. Increased prostanoid production was observed about 8 h after exposure to LPS in hyperosmotic medium compared to Kupffer cells treated with LPS under normotonic (305 mosmol/l) conditions. A similar stimulatory effect of **hyperosmolarity** on PGE2 production was also seen when arachidonate was added exogenously. Hyperosmotic stimulation of PGE2 production was accompanied by a strong induction of Cox-2 mRNA levels and an increase in immunoreactive Cox-2, whereas the levels of immunoreactive phospholipase A2 and cyclooxygenase-1 did not change significantly. Dexamethasone, indomethacin and the selective Cox-2 inhibitor, NS-398, abolished the hypertonicity-induced stimulation of PGE2 formation; dexamethasone also prevented the increase in Cox-2 mRNA and protein. The increase of immunoreactive Cox-2 lasted for about 24 h and was also blocked by actinomycin D or cycloheximide, but not by brefeldin A. Tunicamycin or **treatment** with endoglucosidase H reduced the molecular mass of hypertonicity-induced Cox-2 by 5 kDa. Tunicamycin **treatment** also suppressed the hypertonicity-induced stimulation of PGE2 production. The **hyperosmolarity**/LPS-induced stimulation of prostaglandin formation was partly sensitive to protein kinase C inhibition but was not accompanied by an increase in the cytosolic free Ca2+ concentration. The data suggest that osmolarity may be a critical factor in the regulation of Cox-2 expression and prostanoid production in activated rat liver macrophages.

L36 ANSWER 17 OF 22 CAPLUS COPYRIGHT 2004 ACS on STN

AB Addition of tert butylhydroperoxide (TBHP) (0.2 mM) to perfused rat liver led to a net K+ release of 7.2 μmol/g within 8 min and a net K+ reuptake of 6.6 μmol/g following withdrawal of the hydroperoxide, in line with earlier findings by H. Sies et al. (1974). Net K+ release roughly paralleled the amount of GSSG released from the liver under the influence of the hydroperoxide. The TBHP-induced K+ efflux was inhibited by approx. 70% in the presence of Ba2+ (1 mM), by 30% in Ca2+-free perfusions and was decreased by 50-60% when the intracellular Ca2+ stores were simultaneously depleted by repeated addns. of phenylephrine. TBHP-induced K+ efflux was accompanied by a decrease of the intracellular water space by 58 μL/g ,corresponding to a 10% cell shrinkage. The effect of TBHP on cell volume was inhibited by 70-80% in the presence of Ba2+. In isolated rat hepatocytes **treatment** with TBHP caused a slight hyperpolarization of the membrane at concns. of 100 nM, but marked hyperpolarization occurred at concns. above 10 μM. TBHP (0.2 mM) transiently increased the portal-perfusion pressure by 3.3 cm H2O , due to a slight stimulation of prostaglandin D2 release under the influence of the hydroperoxide. In the presence of Ba2+ (1 mM), TBHP increased the perfusion pressure by 12.7 cm H2O and produced an approx. ten-fold increase of prostaglandin D2 and thromboxane B2 release. Under these conditions, glucose output from the liver rose from 0.9 to 2.9 μmol · g-1 · min-1 with a time course resembling that of portal-pressure increase and prostaglandin D2 overflow. These effects were largely abolished in the presence of ibuprofen or the thromboxane-receptor-**antagonist** BM 13,177. The TBHP effects on perfusion pressure, glucose and eicosanoid output were also enhanced in the presence of insulin or during hypotonic exposure; i.e. conditions known to swell hepatocytes, but not during hyperosmotic exposure. The data suggest that TBHP induces liver cell shrinkage and hyperpolarization of the plasma membrane due to activation of Ba2+-sensitive K+ channels.

L36 ANSWER 18 OF 22 MEDLINE on STN

94291146. PubMed ID: 7912653. [Protection of the ischemic myocardium]. La protezione del miocardio ischemico. Zucchi R; Yu G; Ronca-Testoni S; Ronca G; Mariani M. (Istituto di Cardiologia, Universita degli Studi, Pisa.) Cardiologia (Rome, Italy), (1993 Dec) 38 (12 Suppl 1) 81-9. Ref: 56. Journal code: 8506637. ISSN: 0393-1978. Pub. country: Italy. Language: Italian.

AB The Authors review several pharmacological interventions aimed at protecting the ischemic myocardium. Drugs which have been widely used in the **treatment** of ischemic heart diseases, such as beta-blockers, nitrates and calcium-**antagonists**, are able to delay the development of ischemic injury if administered before the beginning of ischemia, but their clinical effectiveness is limited. The new drugs which are presently investigated are designed to counteract the molecular mechanisms which mediate irreversible tissue injury, namely cytosolic calcium overload, cellular **hyperosmolarity**, and free radical production. In particular, interventions able to interfere with the release of calcium from its intracellular stores would be of major importance. In this regards, it is interesting to point out that derivatives of phenylalkylamine calcium-**antagonists** have been reported to modulate the opening probability of sarcoplasmic reticulum calcium channels.

L36 ANSWER 19 OF 22 EMBASE on STN

91241489 EMBASE Document No.: 1991241489. [Acute diabetic complications].

depends on the intensity of **treatment**. Ketoacidosis and hyperosmolar coma are characterized by hyperglycemia, volume and electrolyte depletion. In ketoacidosis, absolute insulin deficiency (type I diabetes) leads to massive lipolysis from adipose tissue generating free fatty acids which are eventually converted to ketone bodies by the liver. Acidosis results from ketone body accumulation. In type II diabetes, residual endogenous insulin secretion partially prevents lipolysis thereby limiting ketosis.

L36 ANSWER 20 OF 22 MEDLINE on STN DUPLICATE 3
88024309. PubMed ID: 2822056. Calmodulin antagonistic action of the cerebral circulation improver 6,7-dimethoxy-1-(3,4-dimethoxybenzyl)-4-([4-(2-methoxyphenyl)-1-piperazinyl]methyl)isoquinoline. Nakajima T; Okada T; Kuruma I; Yoshizaki H; Satoh T; Kuwahara T; Nakamura K. (Department of Pharmacology, Nippon Roche Research Center, Kamakura, Japan.) Arzneimittel-Forschung, (1987 Jun) 37 (6) 674-9. Journal code: 0372660. ISSN: 0004-4172. Pub. country: GERMANY, WEST: Germany, Federal Republic of. Language: English.

AB 6,7-Dimethoxy-1-(3,4-dimethoxybenzyl)-4-([4-(2-methoxyphenyl)-1-piperazinyl]methyl)isoquinoline (Ro 22-4839) is a new cerebral circulation improver with vasospasmolytic properties. Preliminarily, Ro 22-4839-induced arterial relaxation was confirmed under the **treatment** of various constrictors and it was hardly overcome by addition of extra calcium. In this study the mode and site of action of this agent were further explored. Ro 22-4839 was found to more strongly inhibit the superprecipitation of chicken gizzard smooth muscle actomyosin (IC50 = 2.0 mumol/l) than trifluoperazine (38 mumol/l) and W-7 (N-(6-aminohexyl)-5-chloro-1-naphthalene-sulfonamide) (220 mumol/l), an in vitro model for relaxation-contraction coupling of the smooth muscle in which calmodulin is known to play an important role through phosphorylation of myosin light chain kinase. The calmodulin antagonistic action of Ro 22-4839 was also demonstrated in other calmodulin-related reaction systems such as phosphodiesterase and hydrophobic fluorescent probe, but was very weak in Ca2+, Mg2+-ATPase of rat erythrocyte membrane. Thus, Ro 22-4839 was suggested to have a relative preference for smooth muscle contraction process unlike trifluoperazine and W-7. Moreover, Ro 22-4839 prevented the decrease in erythrocyte deformability induced by **hyperosmolarity** or intracellular Ca2+ accumulation, like trifluoperazine and W-7. However, Ro 22-4839 itself caused hardly an internal stomatocytic shape of erythrocytes in contrast to known calmodulin **antagonists**. Further, Ro 22-4839 inhibited erythrocyte membrane rupture, platelet aggregation and lipid peroxidation.(ABSTRACT TRUNCATED AT 250 WORDS)

L36 ANSWER 21 OF 22 MEDLINE on STN DUPLICATE 4
80225433. PubMed ID: 6771176. Role of calcium influx in the regulation of sugar transport in resting left atrial muscle. Bihler I; Sawh P C. Molecular and cellular endocrinology, (1980 Jul) 19 (1) 93-100. Journal code: 7500844. ISSN: 0303-7207. Pub. country: Netherlands. Language: English.

AB The role of external Ca2+ in the regulation of sugar transport in isolated resting atria of rats and guinea pigs was studied by measuring the tissue/medium distribution of 14C-labelled 3-methylglucose and of 45Ca. Omission of Ca2+ from the medium strongly antagonized the stimulation of sugar transport by insulin, **hyperosmolarity** (100 mM mannitol) or Na+-pump inhibition (K+-free medium). Basal sugar transport was not [illegible] increased when 0.5 mM EGTA was also

were both antagonized by [illegible]
the important role of Ca2+ influx in the control of sugar transport by hormonal and other modulators and are consistent with the hypothesis that cytoplasmic Ca2+ regulates glucose transport in muscle.

L36 ANSWER 22 OF 22 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
75145376 EMBASE Document No.: 1975145376. [Canrenoate potassium in the **treatment** of hyperosmolal syndromes in resuscitation]. IL CANRENOATO DI POTASSIO NEL TRATTAMENTO DELLE SINDROMI IPEROSMOLALI IN RIANIMAZIONE. Gasperi A.; Domenichini E.; Ruozi P.; Bobbio Pallavicini F.. Catt. Anestesiol., Rianim. Univ. Pavia, Italy. Minerva Anestesiologica 40/9 (448-454) 1974.
CODEN: MIANAP. Language: Italian.
AB The osmoregulating effect of a new water soluble aldosterone **antagonist** (canrenoate potassium) was evaluated by intravenously administering it to a group of patients with hyperosmolal syndromes at the dose of 600 mg/day (one 200 mg vial every 8 hr) for 6 days. A progressive diminution of the plasma osmolality was matched by a parallel increase of the urine osmolality. A marked increase of the urinary excretion of sodium was also seen, with retention of potassium and consequent increase of the urinary Na/K ratio. Also the diuresis was significantly influenced by canrenoate K (Soldactone) which was very well tolerated by all cases both locally and generally.

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=> s dehydration
L37     157361 DEHYDRATION

=> s l37 and vasopressin
L38       3806 L37 AND VASOPRESSIN

=> s l38 and treatment
L39        479 L38 AND TREATMENT

=> s l39 and PTHrP antagonist
L40          0 L39 AND PTHRP ANTAGONIST

=> s l39 and "PTHrP"
L41          5 L39 AND "PTHRP"

=> dup remove l41
PROCESSING COMPLETED FOR L41
L42          1 DUP REMOVE L41 (4 DUPLICATES REMOVED)

=> d l42 cbib abs

L42 ANSWER 1 OF 1     MEDLINE on STN                    DUPLICATE 1
2003282974.    PubMed ID: 12810532.   Centrally administered tuberoinfundibular peptide of 39 residues inhibits arginine vasopressin release in conscious rats. Sugimura Yoshihisa; Murase Takashi; Ishizaki Seiji; Tachikawa Kazushige; Arima Hiroshi; Miura Yoshitaka; Usdin Ted B; Oiso Yutaka. (Department of Internal Medicine, Graduate School of Medicine, Nagoya University, Nagoya, Aichi 466-8550, Japan. ) Endocrinology, (2003 Jul) 144 (7) 2791-6.  Journal code: 0375040. ISSN: 0013-7227. Pub. country: United States. Language: English.
AB   Tuberoinfundibular peptide of 39 residues (TIP39) is a recently discovered
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study, [illegible]
TIP39 on AVP release in conscious rats. Intracerebroventricular administration of TIP39 (10-500 pmol/rat) significantly suppressed the plasma AVP concentration in dehydrated rats, and the maximum effect was obtained 5 min after administration (**dehydration** with 100 pmol/rat TIP39, 4.32 +/- 1.17 pg/ml; vs. control, 8.21 +/- 0.70 pg/ml). The plasma AVP increase in response to either hyperosmolality [ip injection of hypertonic saline (HS), 600 mosmol/kg] or hypovolemia [ip injection of polyethylene glycol (PEG)] was also significantly attenuated by an intracerebroventricular injection of TIP39 (HS with 100 pmol/rat TIP39, 2.65 +/- 0.52 pg/ml; vs. HS alone, 4.69 +/- 0.80 pg/ml; PEG with 100 pmol/rat TIP39, 4.10 +/- 0.79 pg/ml; vs. PEG alone, 6.19 +/- 0.34 pg/ml). **Treatment** with naloxone [1.5 mg/rat, sc injection], a nonselective opioid receptor antagonist, significantly reversed the inhibitory effects of TIP39 on AVP release. These results suggest that central TIP39 plays an inhibitory role in the osmoregulation and baroregulation of AVP release and that intrinsic opioid systems are involved in its mechanism.

=> s l38 and lower level
L43 4 L38 AND LOWER LEVEL

=> dup remove l43
PROCESSING COMPLETED FOR L43
L44 3 DUP REMOVE L43 (1 DUPLICATE REMOVED)

=> d l44 1-3 cbib abs

L44 ANSWER 1 OF 3 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN
2001351934 EMBASE Prolonged exercise following diuretic-induced hypohydration effects on fluid and electrolyte hormones. Roy B.D.; Green H.J.; Burnett M.. H.J. Green, Department of Kinesiology, University of Waterloo, 200 University Avenue West Waterloo, Waterloo, Ont. N2L 3G1, Canada. green@healthy.uwaterloo.ca. Hormone and Metabolic Research 33/9 (540-547) 2001.
Refs: 31.
ISSN: 0018-5043. CODEN: HMMRA2. Pub. Country: Germany. Language: English. Summary Language: English.
AB To investigate the hypothesis that a reduction in plasma volume (PV) induced by diuretic administration would result in an increase in the fluid and electrolyte hormonal response to exercise, ten untrained males (VO(2) peak = 3.96±0.41/rain) performed 60 min of cycle ergometry at 61% VO(2) peak twice. The test was carried out once under control conditions (CON) (placebo) and once after 4 days of diuretic administration (DIU) (Novotriamazide; 100 mg triamterene and 50 mg hydrochlorothiazide), Calculated resting PV decreased by 14.6±3.3% (p<0.05) with DIU. No difference in plasma osmolality was observed between conditions. For the hormones measured, differences (p<0.05) between conditions at rest were noted for plasma renin activity (PRA) (0.62±0.09 vs. 5.61±0.94 ng/ml/h), angiotensin I (ANG 1) (0.26±0.03 vs. 0.56±0.08ng/ml), aldosterone (ALD) (143±14 vs. 1603±302 pg/ml), arginine **vasopressin** (AVP) (4.13±1.1 vs. 9.58±1.6 pg/ml) and atrial natriuretic pepide (α-ANP) (11.5±2.8 vs. 6.33±1.0pg/ml). The exercise resulted in increases (p<0.05) in PRA, ANG I, ALD, AVP, α-ANP, DIU led to higher levels of

and a greater increase during exercise [illegible]
effect of DIU only manifested itself during exercise. In contrast, the lower α-ANP observed during exercise with DIU was due to the lower resting levels. These results support the hypotheses that hypohydration leads to alterations in the secretion of all of the fluid and electrolyte hormones with the exception of AVP. The specific mechanisms of these alterations remain unclear, but appear to be related directly to the decrease in PV.

L44 ANSWER 2 OF 3 MEDLINE on STN
90197560. PubMed ID: 2698142. The importance of thirst in maintenance of fluid balance. Ramsay D J. Bailliere's clinical endocrinology and metabolism, (1989 Aug) 3 (2) 371-91. Ref: 82. Journal code: 8704785. ISSN: 0950-351X. Pub. country: ENGLAND: United Kingdom. Language: English.
AB Plasma osmolality is maintained within very narrow limits by the control of water intake via thirst and water output via secretion of **vasopressin**. Osmoreceptors are situated in the brain, but on the blood side of the blood-brain barrier in a circumventricular organ. These regions are stimulated by an increase in plasma osmolality and form the most important input to cause thirst and drinking. Cardiopulmonary and arterial baroreceptors sensitive to blood volume and blood pressure also can be important, so hypovolaemic events such as haemorrhage can stimulate thirst. Both raised plasma osmolality and reduced blood volume contribute to thirst and **vasopressin** secretion following water deprivation. The importance of the nucleus medianus in the neural circuitary involved in integrating thirst should be emphasized. Mechanisms which stop drinking are different from those which initiate it, and oropharyngeal metering of the volume of fluid consumed provides the important input. There are a number of situations in humans where thirst thresholds and sensitivities are altered. The elderly have higher thirst thresholds and this can cause symptoms of **dehydration**. Increased drinking is seen in congestive heart failure, renal hypertension and certain cerebral lesions. Thirst thresholds are set at **lower levels** in pregnancy and in the luteal phase of the menstrual cycle and may contribute to fluid retention in these situations.

L44 ANSWER 3 OF 3 MEDLINE on STN DUPLICATE 1
76167841. PubMed ID: 1262438. The interaction of blood osmolality and blood volume in regulating plasma **vasopressin** in man. Robertson G L; Athar S. Journal of clinical endocrinology and metabolism, (1976 Apr) 42 (4) 613-20. Journal code: 0375362. ISSN: 0021-972X. Pub. country: United States. Language: English.
AB The effect of blood volume on the osmotic control of the antidiuretic hormone, arginine **vasopressin** (AVP), has been studied in 18 healthy young adults. Changes in blood osmolality and/or volume were produced by each of 3 procedures--fluid deprivation, orthostasis, and hypertonic saline infusion--and the resultant changes in plasma AVP were measured by radioimmunoassay and expressed as a function of the simultaneous level of plasma osmolality. When the subjects were hydropenic and recumbent, a highly significant correlation between plasma AVP and osmolality was observed that was described by the regression equation $y = 0.35 (x - 281.0)$ where y represents the plasma AVP concentration in pg/ml and x the plasma osmolality in mosmol/kg. When these same hydropenic subjects were studied in the upright position, a maneuver that reduces intrathoracic blood volume, plasma AVP and osmolality still showed a significant correlation, but the regression equation describing this relation, $y = 0.31 (x - 277.8)$, occupied a

hydropenic conditions. These results [illegible]
decreases in blood volume do influence the osmoregulation of AVP in man, but the effects are relatively small and limited to adjustments in the set of the receptor toward higher or **lower levels** of osmolality.

```
=> s antidiuretic
L45      23957 ANTIDIURETIC

=> s l45 and PTHrP antagonist
L46          0 L45 AND PTHRP ANTAGONIST

=> s l45 and AVP
L47       2113 L45 AND AVP

=> s l47 and antagonist
L48        714 L47 AND ANTAGONIST

=> s l48 and PTHrP
L49          0 L48 AND PTHRP

=> s l48 and antibody
L50          2 L48 AND ANTIBODY

=> dup remove l50
PROCESSING COMPLETED FOR L50
L51           2 DUP REMOVE L50 (0 DUPLICATES REMOVED)

=> d l51 1-2 cbib abs

L51  ANSWER 1 OF 2  SCISEARCH  COPYRIGHT 2004 THOMSON ISI on STN
93:292062   The Genuine Article (R) Number: KZ809. CYTOPLASMIC AND NUCLEAR
     SIGNALING PATHWAYS OF V-1-VASCULAR VASOPRESSIN RECEPTORS.  THIBONNIER M
     (Reprint); BAYER A L; LENG Z H. CASE WESTERN RESERVE UNIV, SCH MED, DEPT
     MED, DIV ENDOCRINOL & HYPERTENS, 10900 EUCLID AVE, CLEVELAND, OH, 44106
     (Reprint); UNIV HOSP CLEVELAND, DEPT INTERNAL MED, DIV ENDOCRINOL &
     HYPERTENS, CLEVELAND, OH, 44106. REGULATORY PEPTIDES (29 APR 1993) Vol.
     45, No. 1-2, pp. 79-84. ISSN: 0167-0115. Pub. country: USA. Language:
     ENGLISH.
     *ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS*
AB      We studied the cytoplasmic and nuclear signaling pathways of
     V1-vascular AVP receptors of human platelets, primary cultures
     of renal glomerular mesangial cells, and established cultures of the A7r5
     aortic smooth muscle cell line.
        The immediate transmembrane signals are triggered by the formation of
     ligand-receptor complexes as illustrated by binding experiments with
     [HS-3]AVP (K(d) = 2.50 nM), d(CH2)5Tyr(Me)AVP (K(d) =
     0.62 nM), the linear V1 antagonist phenylacetyl-D-Tyr(Et)-Phe-
     Val-Asn-Lys-Pro-[I-125]Tyr-NH2 (K(d) = 1.42 nM) or by fluorescence
     experiments with linear antagonists like phenylacetyl-D-Tyr(Et)-
     Phe-Gln-Asn-Lys-Pro-Arg-NH2 coupled to biotin and made fluorescent by
     labeling with tetramethylrhodamine-avidin.
        We used several approaches (radioreceptor binding, radioactive
     labeling, autoradiographic, enzymatic, photoaffinity labeling, and
     immunoblotting procedures) to identify the guanine nucleotide regulatory
     protein coupled to V1-vascular vasopressin receptors. AVP
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V1-vascular **antagonist** d(CH2)5Tyr(Me)**AVP** and [illegible]
was completely abolished by GTP(gammaS). Immunoblotting of platelet proteins with various **antibodies** specific for the C-terminal of the alpha subunits of the three families of G proteins revealed that the 42 kDa protein labeled with [alpha-P-32]azidoanilido GTP was specifically labeled only by **antibodies** specific for the alpha subunit of G. thus suggesting that V1-vascular **AVP** receptors are coupled in a divalent cation-dependent manner to a G protein belonging to the G(q/11) family.

V1-vascular **AVP** receptors activate not only phospholipases C and D but also phospholipase A2. In fura-2 loaded A7r5 cells, the phospholipase A2 inhibitor aristolochic acid reduced **AVP**-induced [Ca2+]i transients. The role of arachidonic acid (AA) metabolites in **AVP**-induced calcium mobilization was precised as follows. AA potentiated **AVP**-induced influx of extracellular Ca2+ and mobilization of intracellular Ca2+. The cyclooxygenase inhibitor indomethacin reduced AA- and **AVP**-induced influx of extracellular Ca2+ but not intracellular Ca2+ mobilization. **AVP**-induced [Ca2+]i transients were not altered by lipoxygenase inhibitors but were reduced in a dose-dependent fashion by ketoconazole, an inhibitor of cytochrome P-450 epoxygenases. The inhibitory action of ketoconazole was noted both in the presence and absence of extracellular Ca2+. Among different epoxygenase metabolites tested, 5,6-epoxyeicosatricnoic acid (5,6-EET) potentiated **AVP**-induced [Ca2+]i transients. Reverse-phase HPLC analysis of lipid extracts from A7r5 cells prelabeled with [C-14]AA isolated a radioactive peak eluting with epoxygenase products. This peak was increased after **AVP** stimulation and blocked by ketoconazole. Gas chromatography-mass spectrometry analysis of cell extracts isolated a compound with epoxyeicosatrienoic characteristics.

The secondary nuclear signaling pathways of V1-vascular **AVP** receptors modulate gene expression. To investigate whether vasopressin (**AVP**) modulates immediate-early gene expression associated with growth in vascular smooth muscle cells, the expression of the proto-oncogenes c-fos and c-jun was studied in cultured A7r5 aortic smooth muscle cells made quiescent by being grown in serum-free media for 48 hs. **AVP** stimulation (10(-12) to 10(-6) M) of A7r5 cells raised in a dose-dependent fashion mRNA levels of c-fos and c-jun without altering the expression of the constitutive gene GAPDH. **AVP** induction of c-fos and c-jun mRNA expression was rapid and transient as it was over within 3 hs. **AVP** effect was specific and blocked by the V1-vascular **antagonist** d(CH2)5Tyr(Me)**AVP**. The mRNA stimulating action of **AVP** required the presence of Ca2+ and involved activation of phospholipases A2 and C as well as protein kinase C.

All these cytoplasmic and nuclear signals explain the major cellular effects of activation of V1-vascular **AVP** receptors, i.e., cell contraction and growth.

L51 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2004 ACS on STN
1985:540008 Document No. 103:140008 Monoclonal **antibodies** to **antidiuretic** hormone. Jones, C. A.; Zamboni, G.; Hanley, M. R. (Dep. Biochem., Imp. Coll., London, SW7 2AZ, UK). Regulatory Peptides (Suppl. 4), 71-3 (English) 1985. CODEN: REPPDY. ISSN: 0167-0115.

AB A mouse monoclonal **antibody**, F439, with unusual specificity and sensitivity for arginine vasopressin (**AVP**) was produced by standard hybridoma technol. F439 was quite specific for **AVP**; binding to

L52 [illegible]
OR AZUMA Y?/AU)

=> s l52 and PTHrP antagonist
L53 0 L52 AND PTHRP ANTAGONIST

=> s l52 and AVP
L54 42 L52 AND AVP

=> dup remove l54
PROCESSING COMPLETED FOR L54
L55 16 DUP REMOVE L54 (26 DUPLICATES REMOVED)

=> d l55 1-16 cbib abs

L55 ANSWER 1 OF 16 MEDLINE on STN DUPLICATE 1
1998187773. PubMed ID: 9528924. Regulation of vasopressin synthesis and release by area postrema in rats. Arima H; Kondo K; Murase T; Yokoi H; Iwasaki Y; **Saito H**; Oiso Y. (First Department of Internal Medicine, Nagoya University School of Medicine, Japan.. harima-ngy@umin.u-tokyo.ac.jp) . Endocrinology, (1998 Apr) 139 (4) 1481-6. Journal code: 0375040. ISSN: 0013-7227. Pub. country: United States. Language: English.

AB There is evidence indicating that the area postrema (AP), the most caudal circumventricular organ located on the dorsal surface of the medulla, is involved in several physiological regulations. In this study, we investigated the role of AP in the regulation of arginine vasopressin (**AVP**) synthesis and release, using rats of which the AP was lesioned 6 weeks previously. The level of plasma **AVP** in the AP lesioned (APX) group was significantly lower than in the sham operated (Sham) group in the basal state. **AVP** release induced by either hyperosmolality or hypovolemia was significantly attenuated by APX. To clarify the role of AP in **AVP** synthesis in the hypothalamus, we examined the **AVP** gene expression using in situ hybridization. **AVP** messenger RNA levels in paraventricular (PVN) and supraoptic nuclei (SON) in the APX group were significantly lower than in the Sham group in the basal state. Moreover, the **AVP** messenger RNA levels in PVN and SON in the APX group were also significantly lower than in the Sham group after water deprivation for 3 days. These results suggest that **AVP** synthesis and release are tonically stimulated by AP in the basal state and that **AVP** synthesis and release in stimulated states are also regulated, at least partially, by AP.

L55 ANSWER 2 OF 16 CAPLUS COPYRIGHT 2004 ACS on STN
1998:372909 Document No. 129:93957 Meniere's disease and vasopressin. Takeda, Taizo; Takeda, Setsuko; **Saito, Haruo**; Kakiki, Akinobu; Nishiyama, Shouji (Dep. Otolaryngol., Kochi Med. Sch., Nankoku, 783-8505, Japan). Otology Japan, 8(2), 58-63 (Japanese) 1998. CODEN: OTJAEW. ISSN: 0917-2025. Publisher: Nippon Jika Gakkai.

AB Recently, a considerable accumulation of evidence has been presented which suggests a possible hormonal control of the inner ear. Vasopressin or corticosteroid may play an important role in the regulation of ion and water. In the present report, it was clin. and exptl. examined how the excess of these hormones might cause any influences on ion and fluid homeostasis in the inner ear. The clin. survey revealed that plasma vasopressin was elevated not only in cases of Meniere's disease but also in cases of the other diseases with endolymphatic hydrops. Especially, it must

the other hand, exptl. induced endolymphatic hydrops reduced by an application of V2-antagonist. Endolymphatic hydrops was also induced by an administration of glucocorticoid as well as by that of aldosterone. Microperoxidase uptake and transport in the marginal cells was accelerated in the animals treated with aldosterone. Since the uptake of microperoxidase is thought to represent water phase endocytosis, aldosterone, a mediator of Na-K ATPase might play a possible role in regulation of water and water-soluble material in the cochlea. These results support the assumption that water and ion regulation in the inner ear is controlled by vasopressin and/or corticosteroids and that the excess of these hormones may be one of the possible factors in the formation of endolymphatic hydrops.

L55 ANSWER 3 OF 16 MEDLINE on STN DUPLICATE 2

95229836. PubMed ID: 7714110. Two novel mutations in the coding region for neurophysin-II associated with familial central diabetes insipidus. Nagasaki H; Ito M; Yuasa H; **Saito H**; Fukase M; Hamada K; Ishikawa E; Katakami H; Oiso Y. (First Department of Internal Medicine, Nagoya University School of Medicine, Aichi, Japan.) Journal of clinical endocrinology and metabolism, (1995 Apr) 80 (4) 1352-6. Journal code: 0375362. ISSN: 0021-972X. Pub. country: United States. Language: English.

AB Familial central diabetes insipidus is an autosomal dominant disease caused by a deficiency of arginine vasopressin (**AVP**). We previously reported three distinct mutations in the **AVP** gene in Japanese familial central diabetes insipidus pedigrees that result in a substitution of Ser for Gly57 in the neurophysin-II (NPII) moiety of the **AVP** precursor, a substitution of Thr for Ala at the COOH-terminus of the signal peptide, and a deletion of Glu47 in the NPII moiety. In this study, we analyzed the **AVP** gene in two pedigrees by direct sequencing of the polymerase chain reaction-amplified DNA and found two novel mutations in exon 2, which encodes the central part of the NPII moiety of the precursor. The mutation in one pedigree was a C to A transition at nucleotide position 1891, which replaces Cys67 (TGC) with stop codon (TGA). As the premature termination eliminates part of the COOH domain of the NPII moiety and the glycoprotein moiety, the conformation of the truncated protein is likely to be markedly different from that of normal precursor. In another pedigree, a G to T transversion was detected at nucleotide position 1874, which substitutes polar Trp (TGG) for hydrophobic Gly62 (GGG). It is possible that mutated NPII molecules, as a consequence of a conformational change, cannot bind **AVP** or self-associate to form higher oligomer complexes. Interestingly, all mutations we have identified to date, with the exception of the signal peptide mutation, are located in exon 2, suggesting the importance of the highly conserved central part of the NPII molecules and/or the NPII moiety in the precursor for **AVP** synthesis.

L55 ANSWER 4 OF 16 MEDLINE on STN DUPLICATE 3

93380921. PubMed ID: 8103767. Glu-47, which forms a salt bridge between neurophysin-II and arginine vasopressin, is deleted in patients with familial central diabetes insipidus. Yuasa H; Ito M; Nagasaki H; Oiso Y; Miyamoto S; Sasaki N; **Saito H**. (First Department of Internal Medicine, Nagoya University School of Medicine, Aichi, Japan.) Journal of clinical endocrinology and metabolism, (1993 Sep) 77 (3) 600-4. Journal code: 0375362. ISSN: 0021-972X. Pub. country: United States. Language: English.

sequence analysis, polymerase chain reaction-amplified fragments including the region were subcloned and sequenced. A 3-basepair deletion (AGG) out of two consecutive AGG sequences (nucleotides 1824-1829) was identified in one of two alleles. The cosegregation of the mutation with the DI phenotype in the family was confirmed by restriction enzyme analyses. This mutation should yield an abnormal **AVP** precursor lacking Glu47 in its neurophysin-II (NP) moiety. Since Glu47 is essential for NP molecules to form a salt bridge with **AVP**, it is very likely that the function of NP as a carrier protein for **AVP** would be impaired. We suggest that **AVP** would undergo accelerated proteolytic degradation, and this mechanism would be involved in the pathogenesis of DI in this pedigree.

L55 ANSWER 5 OF 16 CAPLUS COPYRIGHT 2004 ACS on STN
1992:4381 Document No. 116:4381 Ion channel activities of cultured rat mesangial cells. Matsunaga, Hiroshi; Yamashita, Naohide; Miyajima, Yoshihiro; Okuda, Toshihiro; Chang, Hangil; **Ogata, Etsuro;** Kurokawa, Kiyoshi (Sch. Med., Univ. Tokyo, Tokyo, 113, Japan). American Journal of Physiology, 261(5, Pt. 2), F808-14 (English) 1991. CODEN: AJPHAP. ISSN: 0002-9513.

AB The patch-clamp technique was used to clarify the nature of ion channels in renal mesangial cells in culture. In the cell-attached mode most patches were silent in the absence of agonists. In some patches a 25-pS nonselective channel was observed This 25-pS cation channel was consistently observed in inside-out patches, and it was activated by intracellular Ca2+. Excised patch expts. also revealed the existence of a 40-pS K+ channel, which was activated by intracellular Ca2+. This 40-pS K+ channel was observed infrequently in the cell-attached mode. The activities of both channels were increased by arginine vasopressin or angiotensin II, resulting from an increase in intracellular Ca2+ concentration

L55 ANSWER 6 OF 16 MEDLINE on STN DUPLICATE 4
91123474. PubMed ID: 1840604. A single base substitution in the coding region for neurophysin II associated with familial central diabetes insipidus. Ito M; Mori Y; Oiso Y; **Saito H.** (First Department of Internal Medicine, Nagoya University School of Medicine, Japan.) Journal of clinical investigation, (1991 Feb) 87 (2) 725-8. Journal code: 7802877. ISSN: 0021-9738. Pub. country: United States. Language: English.

AB To elucidate the molecular mechanism of familial central diabetes insipidus (FDI), we sequenced the arginine vasopressin-neurophysin II (**AVP**-NPII) gene in 2 patients belonging to a pedigree that is consistent with an autosomal dominant mode of inheritance. 10 patients with idiopathic central diabetes insipidus (IDI) and 5 normals were also studied. The **AVP**-NPII gene, locating on chromosome 20, consists of three exons that encode putative signal peptide, **AVP**, NPII, and glycoprotein. Using polymerase chain reaction, fragments including the promoter region and all coding regions were amplified from genomic DNA and subjected to direct sequencing. Sequences of 10 patients with IDI were identical with those of normals, while in 2 patients with FDI, a single base substitution was detected in one of two alleles of the **AVP**-NPII gene, indicating they were heterozygotes for this mutation. It was a G----A transition at nucleotide position 1859 in the second exon, resulting in a substitution of Gly for Ser at amino acid position 57 in the NPII moiety. It was speculated that the mutated **AVP**-NPII precursor or the mutated NPII molecule, through their conformational changes, might be responsible for **AVP** deficiency.

(1991) Vol. 87, No. 2, pp. 725-728. Pub. country: JAPAN. Language: ENGLISH

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB To elucidate the molecular mechanism of familial central diabetes insipidus (FDI), we sequenced the arginine vasopressin-neurophysin II (**AVP**-NPII) gene in 2 patients belonging to a pedigree that is consistent with an autosomal dominant mode of inheritance. 10 patients with idiopathic central diabetes insipidus (IDI) and 5 normals were also studied. The **AVP**-NPII gene, locating on chromosome 20, consists of three exons that encode putative signal peptide, **AVP**, NPII, and glycoprotein. Using polymerase chain reaction, fragments including the promoter region and all coding regions were amplified from genomic DNA and subjected to direct sequencing. Sequences of 10 patients with IDI were identical with those of normals, while in 2 patients with FDI, a single base substitution was detected in one of two alleles of the **AVP**-NPII gene, indicating they were heterozygotes for this mutation. It was a G --> A transition at nucleotide position position 1859 in the second exon, resulting in a substitution of Gly for Ser at amino acid positions 57 in the NPII moiety. It was speculated that the mutated **AVP**-NPII precursor of the mutated NPII molecule, through their conformational changes, might be responsible for **AVP** deficiency.

L55 ANSWER 8 OF 16 MEDLINE on STN DUPLICATE 5

92026457. PubMed ID: 1718168. Endothelin 1 increases cell calcium in mouse collecting tubule cells. Naruse M; Uchida S; **Ogata E**; Kurokawa K. (First Department of Internal Medicine, University of Tokyo Faculty of Medicine, Japan.) American journal of physiology, (1991 Oct) 261 (4 Pt 2) F720-5. Journal code: 0370511. ISSN: 0002-9513. Pub. country: United States. Language: English.

AB Effects of endothelin 1 (ET-1) on intracellular free calcium concentration ([Ca2+]i) were examined in superfused single-nephron segments dissected from mouse kidney. ET-1, 10(-9) to 10(-6) M, caused a biphasic increase in [Ca2+]i consisting of an initial rapid rise followed by a second more sustained elevation in [Ca2+]i in cortical collecting tubules (CCT), outer medullary CT (OMCT), and inner medullary CT (IMCT). The magnitude of the response was dose dependent and was greater in CCT than in OMCT or IMCT. Additional studies using CCT revealed that Ca2+ removal from the superfusate resulted in attenuation of the second phase of [Ca2+]i with approximately 50% reduction in the height of the initial [Ca2+]i peak in response to 10(-6) M ET-1. Ca2+ channel blocker nicardipine had little effect on ET-1-evoked changes in [Ca2+]i. BAY K 8644 and high superfusate K+ also did not affect [Ca2+]i. Addition of ET-1 and arginine vasopressin (**AVP**), 10(-6) M each, showed the presence of homologous desensitization but the absence of heterologous desensitization in [Ca2+]i changes. There was no additive effect of ET-1 and **AVP** on [Ca2+]i when they were added together. These data show that ET-1 evokes a biphasic increase in [Ca2+]i of collecting tubules and suggest that the initial peak of the ET-1-evoked rise in [Ca2+]i is largely due to cell Ca2+ release and that the second sustained rise in [Ca2+]i is largely due to increased Ca2+ influx. Data also suggest that ET-1 and **AVP** may act in the collecting tubules through different receptors.

L55 ANSWER 9 OF 16 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN

91:584382 The Genuine Article (R) Number: GK869. ENDOTHELIN-1 INCREASES CELL CALCIUM IN MOUSE COLLECTING TUBULE CELLS. NARUSE M; UCHIDA S; **OGATA**

concentration ([Ca2+]i) were examined in [illegible] segments dissected from mouse kidney. ET-1, 10(-9) to 10(-6) M, caused a biphasic increase in [Ca2+]i consisting of an initial rapid rise followed by a second more sustained elevation in [Ca2+]i in cortical collecting tubules (CCT), outer medullary CT (OMCT), and inner medullary CT (IMCT). The magnitude of the response was dose dependent and was greater in CCT than in OMCT or IMCT. Additional studies using CCT revealed that Ca2+ removal from the superfusate resulted in attenuation of the second phase of [Ca2+]i with approximately 50% reduction in the height of the initial [Ca2+]i peak in response to 10(-6) M ET-1. Ca2+ channel blocker nicardipine had little effect on ET-1-evoked changes in [Ca2+]i. BAY K 8644 and high superfusate K+ also did not affect [Ca2+]i. Addition of ET-1 and arginine vasopressin (**AVP**), 10(-6) M each, showed the presence of homologous desensitization but the absence of heterologous desensitization in [Ca2+]i changes. There was no additive effect of ET-1 and **AVP** on [Ca2+]i when they were added together. These data show that ET-1 evokes a biphasic increase in [Ca2+]i of collecting tubules and suggest that the initial peak of the ET-1-evoked rise in [Ca2+]i is largely due to cell Ca2+ release and that the second sustained rise in [Ca2+]i is largely due to increased Ca2+ influx. Data also suggest that ET-1 and **AVP** may act in the collecting tubules through different receptors.

L55 ANSWER 10 OF 16 MEDLINE on STN DUPLICATE 6
90078645. PubMed ID: 2592564. Ambient Cl- ions modify rat mesangial cell contraction by modulating cell inositol trisphosphate and Ca2+ via enhanced prostaglandin E2. Okuda T; Kojima I; **Ogata E**; Kurokawa K. (Fourth Department of Internal Medicine, University of Tokyo School of Medicine, Japan.) Journal of clinical investigation, (1989 Dec) 84 (6) 1866-72. Journal code: 7802877. ISSN: 0021-9738. Pub. country: United States. Language: English.

AB Our recent observation showed that angiotensin II (AII) and arginine vasopressin (**AVP**) stimulate Ca2+-activated Cl- conductance in mesangial cells. These data raise the possibility that mesangial cell function may be modulated by extracellular chloride concentration [(Cl-]o). The present study was undertaken to test this possibility using cultured rat mesangial cells. When the [Cl-]o was reduced to zero, the percentage of mesangial cells showing contraction responding to AII and **AVP** was decreased from 72 +/- 9 to 33 +/- 10% and from 60 +/- 4 to 24 +/- 11%, respectively. Ca2+ transients induced by AII and **AVP** , measured in mesangial cells loaded with Ca2+-sensitive photoprotein aequorin, were attenuated as [Cl-]o decreased. Also, when [Cl-]o decreased, inositol trisphosphate (IP3) levels of mesangial cells were suppressed, both in the presence and absence of AII or **AVP**. PGE2 production by mesangial cells increased when [Cl-]o decreased and the effects of ambient Cl- deprivation could be restored by addition of indomethacin to the Cl- -free medium. Moreover, PGE2 decreased mesangial cell contractility, Ca2+ transients, and IP3 production in response to AII and **AVP**. These data suggest that the decrease in [Cl-]o attenuates mesangial cell contraction by suppressing IP3 production and thus Ca2+ transients in response to AII and **AVP** through enhanced PGE2 production.

L55 ANSWER 11 OF 16 CAPLUS COPYRIGHT 2004 ACS on STN
1989:89450 Document No. 110:89450 Effect of atrial natriuretic peptide on catecholamine release from human pheochromocytoma. Nakamaru, Mitsuaki; Ogihara, Toshio; **Saito, Hiroshi**; Rakugi, Hiromi; Hashizume,

decrease in the mean blood pressure, an increase in the heart rate, and a marked increase in the plasma level of norepinephrine compared with values in normal subjects. Treatment with ANP also increased the plasma epinephrine level in the patients with pheochromocytoma, but not in the normal subjects. After removal of the tumor, the responses of the plasma norepinephrine and epinephrine to **AVP** infusion were normalized. There was no significant effect of 10-8-10-5M ANP on the basal release of catecholamines from isolated superfused pheochromocytoma tissue. ANP (10-7M) did not affect the increase in catecholamine release induced by glucagon (10-5M). Thus, the exaggerated responses of plasma catecholamines to ANP in patients with pheochromocytoma may be due to a washout effect resulting from change in blood flow in the vessels feeding the tumor rather than increased sympathetic nerve activity induced by hypotension and hypovolemia. Evidently, ANP does not have any direct action on pheochromocytoma tissue causing catecholamine release.

L55 ANSWER 12 OF 16 MEDLINE on STN DUPLICATE 7
89219790. PubMed ID: 2710398. Impaired responsiveness of paraventricular neurosecretory neurons to osmotic stimulation in rats after local anesthesia of the subfornical organ. Tanaka J; **Saito H**; Yagyu K. (Department of Physiology, Kochi Medical School, Japan.) Neuroscience letters, (1989 Mar 13) 98 (1) 51-6. Journal code: 7600130. ISSN: 0304-3940. Pub. country: Netherlands. Language: English.

AB Extracellular recordings were obtained from 32 phasically active neurosecretory cells in the hypothalamic paraventricular nucleus (PVN) of urethane-anesthetized male rats. None of the PVN cells changed their activity to intracarotid infusions of isotonic saline (0.15 M NaCl solution, 0.05 ml). Of these PVN neurons, 26 displayed an increase in neuronal activity following intracarotid infusions of hypertonic saline (0.2 M NaCl solution, 0.05 ml), while the remainder were unresponsive. Microinjection of the local anesthetic lidocaine into the subfornical organ (SFO) reversibly diminished the excitatory response to the infusions of hypertonic saline in 10 out of 15 PVN neurons tested, whereas the injection of lidocaine into the vicinity of the SFO (n = 4) or the third ventricle (n = 4) did not cause a marked change. These results show an involvement of the SFO in the mechanism of osmotic activation of putative vasopressin (**AVP**)-secreting neurons in the PVN.

L55 ANSWER 13 OF 16 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
1987:140101 Document No.: PREV198732068736; BR32:68736. ANGIOTENSIN II AII AND VASOPRESSIN **AVP** STIMULATE CALCIUM-ACTIVATED CHLORIDE CONDUCTANCE IN CULTURED RAT MESANGIAL CELLS BY RELEASING CALCIUM FROM INTRACELLULAR ORGANELLAE. OKUDA T [Reprint author]; YAMASHITA N; KOJIMA I; **OGATA E**; KUROKAWA K. IVTH INT MED, UNIV TOKYO SCH MED, TOKYO, JPN. Kidney International, (1987) Vol. 31, No. 1, pp. 282.
Meeting Info.: MEETING OF THE AMERICAN SOCIETY OF NEPHROLOGY, WASHINGTON, D.C., USA, DECEMBER 7-10, 1986. KIDNEY INT.
CODEN: KDYIA5. ISSN: 0085-2538. Language: ENGLISH.

L55 ANSWER 14 OF 16 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
87:17053 The Genuine Article (R) Number: F4838. ANGIOTENSIN-II (AII) AND VASOPRESSIN (**AVP**) STIMULATE CA++-ACTIVATED C1-CONDUCTANCE IN CULTURED RAT MESANGIAL CELLS BY RELEASING CA++ FROM INTRACELLULAR ORGANELLAE. OKUDA T (Reprint); YAMASHITA N; KOJIMA I; **OGATA E**; KUROKAWA K. UNIV TOKYO, SCH MED, DEPT INTERNAL MED 14, TOKYO 113, JAPAN. KIDNEY INTERNATIONAL (1987) Vol. 31, No. 1, pp. 282. Pub. country: JAPAN.

aldosterone excretion rate and urinary [illegible]
rats. Minami M; Togashi H; Sano M; Saito I; Morii K; Nomura A; Yoshioka M; **Saito H.** [Hokkaido igaku zasshi] Hokkaido journal of medical science, (1985 Nov) 60 (6) 856-64. Journal code: 17410290R. ISSN: 0367-6102. Pub. country: Japan. Language: Japanese.

AB Present study was undertaken to elucidate the effects of a new vasodilatating antihypertensive drug, budralazine on water drinking behavior and humoral factors including plasma norepinephrine (NE), angiotensin II (A II), arginine vasopressin (**AVP**), serotonin (5-HT) concentrations, urinary aldosterone and catecholamine excretion rates. After oral budralazine administration (10 mg/kg/day, p.o., for 7 days), systolic tail blood pressure of Wistar Kyoto rats (WKY) decreased significantly. While, heart rate and water drinking activity of WKY significantly increased. Urinary catecholamine excretion rate did not change after oral administration of budralazine (10 mg/kg and 100 mg/kg/day, p.o.; for 7 days). However, significant increase in urinary aldosterone excretion rate was demonstrated. Both plasma A II and NE concentrations tended to increase after oral administration of budralazine (100 mg/kg/day). Plasma **AVP** and 5-HT concentrations were not influenced by budralazine. These findings suggest that budralazine acts on renin angiotensin aldosterone system as compared to that in the sympathetic nervous system.

L55 ANSWER 16 OF 16 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN DUPLICATE 9

86073851 EMBASE Document No.: 1986073851. Neuropeptide and monoamine immunoreactivity of the circadian pacemaker in Periplaneta. Takeda M.; Endo Y.; **Saito H.**; et al.. Entomological Laboratory, Kobe University, Kobe 657, Japan. Biomedical Research 6/6 (395-406) 1985. CODEN: BRESD5. Pub. Country: Japan. Language: English.

AB Immunoreactive neurons were detected in Periplaneta americana in the pacemaker loci of the optic lobe. Approximately ten cells on the dorsal side and about five cells on the ventral side of the clock loci which lie anteriorly to the second optic chiasm reacted with an anti-bovine pancreatic polypeptide (BPP) serum. So did nearly an equal number of cells with an antiserum raised against histidine-isoleucine containing peptide fraction 20-27 (PHI 20-27). Three to five cells were reactive with antisera against gastrin, CCK (1-27), glicentin, β-endorphin and serotonin, with stronger reactivity appearing in the ventral locus. Several antisera reactive with mammalian circadian pacemaker, the suprachiasmatic nuclei (SCN), such as those against vasoactive intestinal polypeptide (VIP), Arg-vasopressin (**AVP**), somatostatin and substance P did not show positive reactions in the cell bodies of the optic lobe, a location of the circadian pacemaker in the cockroach. Optic neuropiles contained materials immunoreactive to antisera against Met-enkephalin, VIP, **AVP**, oxytocin and hydroxy-indole-O-methyltransferase (HIOMT), a melatonin synthesizing enzyme, as well as those which stained perikarya. All antisera that gave a positive response in the optic lobe stained the central body too, though the staining pattern was somewhat different with the antiserum tested.

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FILE 'MEDLINE, EMBASE, BIOSIS, SCISEARCH, CAPLUS' ENTERED AT 08:27:59 ON

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L6              0 S L1 AND HYPEROSMOLARITY
L7              3 S L4 AND VOMITING
L8              1 DUP REMOVE L7 (2 DUPLICATES REMOVED)
L9              3 S L4 AND POLYURIA
L10             1 DUP REMOVE L9 (2 DUPLICATES REMOVED)
L11             3 S L4 AND ANTIHYPERCALCEMIC ACTIVITY
L12             1 DUP REMOVE L11 (2 DUPLICATES REMOVED)
L13            64 DUP REMOVE L4 (136 DUPLICATES REMOVED)
L14             0 S L13 AND HYPEROSMOLARITY
L15            15 S L13 AND "PTHRP 1-34"
L16           112 S PTHRP RECEPTOR ANTAGONIST
L17            22 S L16 AND BINDING
L18             6 S L17 AND ANTIBODY
L19             6 DUP REMOVE L18 (0 DUPLICATES REMOVED)
L20            32 DUP REMOVE L16 (80 DUPLICATES REMOVED)
L21             3 S "#23-57-137-1"
L22             3 DUP REMOVE L21 (0 DUPLICATES REMOVED)
L23          2943 S VASOPRESSIN LEVEL
L24            95 S L23 AND SYMPTOM
L25            12 S L24 AND TREATMENT
L26             4 DUP REMOVE L25 (8 DUPLICATES REMOVED)
L27             9 S POLYURIA TREATMENT
L28             4 S L27 AND VASOPRESSIN
L29             3 DUP REMOVE L28 (1 DUPLICATE REMOVED)
L30             0 S HYPEROSMOLARITY TREATMENT
L31          4102 S HYPEROSMOLARITY
L32             0 S L31 AND DECREASE VASOPRESSIN
L33           646 S L31 AND TREATMENT
L34            34 S L33 AND ANTAGONIST
L35             0 S L34 AND PTHRP
L36            22 DUP REMOVE L34 (12 DUPLICATES REMOVED)
L37        157361 S DEHYDRATION
L38          3806 S L37 AND VASOPRESSIN
L39           479 S L38 AND TREATMENT
L40             0 S L39 AND PTHRP ANTAGONIST
L41             5 S L39 AND "PTHRP"
L42             1 DUP REMOVE L41 (4 DUPLICATES REMOVED)
L43             4 S L38 AND LOWER LEVEL
L44             3 DUP REMOVE L43 (1 DUPLICATE REMOVED)
L45         23957 S ANTIDIURETIC
L46             0 S L45 AND PTHRP ANTAGONIST
L47          2113 S L45 AND AVP
L48           714 S L47 AND ANTAGONIST
L49             0 S L48 AND PTHRP
L50             2 S L48 AND ANTIBODY
L51             2 DUP REMOVE L50 (0 DUPLICATES REMOVED)
L52         32640 S (OGATA E?/AU OR ONUMA E?/AU OR TSUNENARI T?/AU OR SAITO H?/AU
L53             0 S L52 AND PTHRP ANTAGONIST
L54            42 S L52 AND AVP
L55            16 DUP REMOVE L54 (26 DUPLICATES REMOVED)

=> s l52 and "PTHrP"
L56           135 L52 AND "PTHRP"

=> s l56 and antagonist
L57             8 L56 AND ANTAGONIST
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L58 ANSWER 1 OF 8 CAPLUS COPYRIGHT 2004 ACS on STN
2002:888597 Document No. 138:3671 Angiogenesis inhibitors that block binding of PTH-related peptide to its receptor for use as antitumor agents. **Saito, Hidemi; Tsunenari, Toshiaki; Onuma, Etsuro**; Kato, Atsuhiko; Suzuki, Masami (Chugai Seiyaku Kabushiki Kaisha, Japan). PCT Int. Appl. WO 2002092133 A1 20021121, 110 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (Japanese). CODEN: PIXXD2. APPLICATION: WO 2002-JP4586 20020510. PRIORITY: JP 2001-140659 20010510.

AB It is found out that angiogenesis can be inhibited by a substance which inhibits the binding of a parathyroid hormone-associated peptide (e.g. **PTHrP**) to its receptor. The angiogenesis inhibitors can be anti-**PTHrP** antibodies, antibody fragments, humanized or chimeric antibodies, PTH receptor **antagonists**, or antisense oligonucleotides specific to **PTHrP**. These modified anti-**PTHrP** antibodies and PTH receptor **antagonists** are useful as antitumor agents and bone metastasis inhibitors.

L58 ANSWER 2 OF 8 CAPLUS COPYRIGHT 2004 ACS on STN
2001:661283 Document No. 135:240920 Tissue decomposition inhibitor. **Saito, Hidemi; Tsunenari, Toshiaki; Onuma, Etsuro**; Sato, Koh (Chugai Seiyaku K. K., Japan). PCT Int. Appl. WO 2001064249 A1 20010907, 131 pp. DESIGNATED STATES: W: CA, JP, US. (Japanese). CODEN: PIXXD2. APPLICATION: WO 2000-JP5886 20000830. PRIORITY: JP 2000-52414 20000228.

AB A tissue decomposition inhibitor which contains a substance inhibiting the binding of a parathyroid hormone-associated peptide to its receptor. The tissue decomposition inhibitor is a **PTHrP** receptor **antagonist** such as antibody, chimeric antibody, monoclonal antibody, or antibody fragment specifically binds to **PTHrP** receptor. The **PTHrP** receptor **antagonist** is useful for inhibiting decomposition muscle or adipose tissue and elevation of inflammatory cytokine. The **PTHrP** receptor **antagonist** is therefore useful for treating sepsis, trauma, muscle dystrophy, cancer-associated weight loss,.

L58 ANSWER 3 OF 8 CAPLUS COPYRIGHT 2004 ACS on STN
2001:31355 Document No. 134:99582 Remedies for drug-resistant hypercalcemia. **Saito, Hidemi; Tsunenari, Toshiaki; Onuma, Etsuro** (Chugai Seiyaku Kabushiki Kaisha, Japan). PCT Int. Appl. WO 2001002012 A1 20010111, 118 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (Japanese). CODEN: PIXXD2. APPLICATION: WO 2000-JP4523 20000706. PRIORITY: JP 1999-192270 19990706.

AB Remedies for drug-resistant hypercalcemia which contain as the active ingredient a substance inhibiting the binding of a parathyroid

L58 ANSWER 4 OF 8 CAPLUS COPYRIGHT 2004 ACS on STN
2001:31354 Document No. 134:110951 Remedies for diseases caused by PTH or **PTHrP**. **Ogata, Etsuro**; Sato, Koh; **Onuma, Etsuro**; **Tsunenari, Toshiaki**; **Saito, Hidemi**; **Azuma, Yumiko** (Chugai Seiyaku Kabushiki Kaisha, Japan). PCT Int. Appl. WO 2001002011 A1 20010111, 130 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (Japanese). CODEN: PIXXD2. APPLICATION: WO 2000-JP4414 20000703. PRIORITY: JP 1999-189793 19990702.

AB Provided are remedies for diseases caused by PTH or **PTHrP**. These remedies contain, as the active ingredient, an agonist or an **antagonist** binding to PTH receptor or **PTHrP** receptor or a substance binding to a ligand of such a receptor to thereby promote or inhibit the binding of the ligand to the receptor.

L58 ANSWER 5 OF 8 CAPLUS COPYRIGHT 2004 ACS on STN
2001:31353 Document No. 134:114837 Agents for ameliorating low vasopressin level. **Ogata, Etsuro**; **Onuma, Etsuro**; **Tsunenari, Toshiaki**; **Saito, Hidemi**; **Azuma, Yumiko** (Chugai Seiyaku Kabushiki Kaisha, Japan). PCT Int. Appl. WO 2001002010 A1 20010111, 114 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (Japanese). CODEN: PIXXD2. APPLICATION: WO 2000-JP4413 20000703. PRIORITY: JP 1999-189322 19990702.

AB Agents for ameliorating low vasopressin level which contain as the active ingredient a substance capable of inhibiting the binding of a parathyroid hormone-associated peptide to its receptor; and agents for ameliorating symptoms caused by a decrease in vasopressin level which contain as the active ingredient a substance capable of inhibiting the binding of a parathyroid hormone-associated peptide to its receptor.

L58 ANSWER 6 OF 8 CAPLUS COPYRIGHT 2004 ACS on STN
2000:15036 Document No. 132:73627 Therapeutics containing inhibitors for parathyroid hormone-related peptide receptor for hypercalcemic crisis. Sato, Koh; **Tsunenari, Toshiaki** (Chugai Seiyaku Kabushiki Kaisha, Japan). PCT Int. Appl. WO 2000000219 A1 20000106, 120 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (Japanese). CODEN: PIXXD2. APPLICATION: WO 1999-JP3433 19990625. PRIORITY: JP 1998-180143 19980626.

AB Disclosed is a therapeutic composition containing an inhibitor for parathyroid

malignancy. Mouse monoclonal ... derivative hMBC(q) were used to demonstrate their rapid and long-lasting effects on reducing blood Ca level, which are more desirable as compared to calcitonin, in a rat model.

L58 ANSWER 7 OF 8 MEDLINE on STN
2000354698. PubMed ID: 10898333. Parathyroid hormone-related protein as a potential target of therapy for cancer-associated morbidity. **Ogata E.** (Japanese Foundation for Cancer Research, Tokyo.) Cancer, (2000 Jun 15) 88 (12 Suppl) 2909-11. Journal code: 0374236. ISSN: 0008-543X. Pub. country: United States. Language: English.

AB BACKGROUND: Proinflammatory cytokines are involved in the genesis of cancer-associated cachexia. Parathyroid hormone-related protein (**PTHrP**) is the causative agent in humoral hypercalcemia of malignancy (HHM) and is frequently secreted from various kinds of solid tumors as well as from adult T-cell leukemia/lymphoma. **PTHrP**, like PTH, acts on PTH receptor type 1 (PTH1R). Activation of PTH1R may lead to stimulation of secretion of proinflammatory cytokines. It is expected, therefore, that **PTHrP** constitutes a key factor in the activation of the proinflammatory and cachectogenic cytokine network and consequently in the development of cachexia in patients with cancer. METHODS: Two groups of cancer-bearing patients of similar clinical backgrounds were enrolled. Plasma concentrations of **PTHrP** and cytokines were measured with immunoradiometric assay and radioimmunoassay, respectively. Cancer tissues from patients with HHM were transplanted into nude mice or nude rats. The effects of humanized antihuman **PTHrP** antibody were examined. RESULTS: In clinical studies, Group B patients (with elevated plasma **PTHrP**), compared with Group A patients (with normal plasma **PTHrP**), tended to exhibit higher plasma levels of tumor necrosis factor (TNF)-alpha (P = 0.13), interleukin (IL)-5 (P = 0.08), and IL-8 (P = 0.08), and had significantly higher levels of IL-6 (P = < or =0.01). The levels of TNF-alpha and IL-6 correlated with those of **PTHrP**. In animal studies, the antibody caused a prompt and sustained decline in serum calcium. This response was accompanied by improvements in food intake, drinking, body weight gain, and general behavior. It also ameliorated the suppression of serum ADH. When those effects were compared with those induced either by bisphosphonate or calcitonin, it turned out that not all of the beneficial effects of the antibody were directly correlated with the depression of blood calcium. CONCLUSIONS: **PTHrP** is a promising molecular target for the development of a novel mode of treatment for patients with cancer-associated morbidity.

L58 ANSWER 8 OF 8 CAPLUS COPYRIGHT 2004 ACS on STN
1999:734813 Document No. 132:88525 The effect of cytokines on parathyroid hormone-related protein (PTH-rP) production in human amnion cells. Ichizuka, Kiyotake; Morimoto, Taro; Suzuki, Makoto; Sasaki, Yasushi; Kurihara, Hitomi; **Saito, Hiroshi**; Yanaihara, Takumi (Department of Obstetrics and Gynecology, Showa University School of Medicine, Tokyo, 142-8666, Japan). Endocrine Journal (Tokyo), 46(4), 479-486 (English) 1999. CODEN: ENJOEO. ISSN: 0918-8959. Publisher: Japan Endocrine Society.

AB In the present study, the effects of various cytokines on parathyroid hormone-related protein (PTH-rP) production and PTH-rP mRNA expression in human amnion cells were studied. Immunoreactive (ir) PTH-rP was measured by immunoradiometric assay and the expression of PTH-rP mRNA was determined by Northern blot anal. The addition of interleukin-1β (IL-1β, 10

IL-1β was reduced by [illegible]
dose dependent manner. Both tetradecanoyl phorbol acetate (TPA), and forskolin increased PTH-rP mRNA levels and the PTH-rP production in amnion cells, and the effect of TPA was much greater than that of forskolin. The findings of the present study suggest of the participation of inflammatory cytokines for the regulation of PTH-rP production in human amnion cells.

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